19 September 2024
EMA/CHMP/494023/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: Daratumumab

Procedure No. EMEA/H/C/004077/II/0072

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AL amyloidosis	amyloid light chain or primary amyloidosis
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
CCDS	Company Core Data Sheet
CCO	clinical cutoff
CI	confidence interval
Cmax	maximum plasma drug concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
Ctrough	trough plasma concentration (taken directly before next administration)
D Kd	daratumumab, carfilzomib, and dexamethasone
DoR	duration of response
D Pd	daratumumab, pomalidomide, and dexamethasone
D-R	daratumumab and lenalidomide
D Rd	daratumumab, lenalidomide, and dexamethasone
DT	drug tolerant
D-VMP	daratumumab, bortezomib, melphalan, and prednisone
D-VRd	daratumumab, bortezomib, lenalidomide, and dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group Scale of Performance Status
EMA	European Medicines Agency
EMN	European Melanoma Network
E-R	exposure-response
ESMO	European Society for Medical Oncology

EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GHS	Global Health Score
GOF	Goodness of fit
HBV	hepatitis B virus
HLT	high level term
HR	hazard ratio
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IDSMB	Independent Data Safety Monitoring Board
IgG	Immunoglobulin G
IMiD	immunomodulatory imide drug
IMWG	International Myeloma Working Group
IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
KRd	carfilzomib, lenalidomide, and dexamethasone
LS	least squares
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NE	not evaluable
NGS	next generation sequencing
NK	natural killer

NONMEM	Non-linear Mixed Effects Modelling
OR	odds ratio
ORR	overall response rate
OS	overall survival
PABAK	prevalence-adjusted bias-adjusted kappa
Pd	pomalidomide and dexamethasone
PD	progressive disease/disease progression
PFS	progression-free survival
PFS2	progression free survival on/after the next line of therapy
PI	proteasome inhibitor
PR	partial response
PRO	patient reported outcomes
PT	preferred term
R	lenalidomide alone
Rd	lenalidomide and dexamethasone
rHuPH20	recombinant human hyaluronidase PH20
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
sARR	systemic administration-related reaction
SC	subcutaneous
sCR	stringent complete response
SD	standard deviation
SOC	system organ class
SPM	second primary malignancy
TEAE	treatment-emergent adverse event
US	United States
VCd	bortezomib, cyclophosphamide, and dexamethasone
VGPR	very good partial response
VRd	bortezomib, lenalidomide, and dexamethasone
VTd	bortezomib, thalidomide, and dexamethasone

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 6 March 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include, in combination with bortezomib, lenalidomide and dexamethasone, the treatment of adult patients with newly diagnosed multiple myeloma, who are eligible for autologous stem cell transplant for Darzalex, based on the primary analysis results from the pivotal study 54767414MMY3014 (PERSEUS) and the results from study 54767414MMY2004 (GRIFFIN) and the D-VRd cohort of study 54767414MMY2040 (PLEIADES).
MMY3014 (PERSEUS) is a randomised, open-label, active-controlled, multicentre phase 3 study in adult subjects with newly diagnosed multiple myeloma, who are eligible for high dose therapy (as required for autologous stem cell transplant). The primary objective is to compare the efficacy of (subcutaneous) daratumumab in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) versus bortezomib, lenalidomide and dexamethasone (VRd) in terms of progression free survival (PFS).
MMY2004 (GRIFFIN) is a randomised, open-label, active controlled, multicentre phase 2 study in adult subjects with newly diagnosed multiple myeloma, who are eligible for high dose therapy and autologous stem cell transplant. The primary objective is to compare the efficacy of daratumumab in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) versus bortezomib, lenalidomide and dexamethasone (VRd), in terms of stringent complete response (sCR) rate.
MMY2040 (PLEIADES) is a randomised, open-label, multicentre phase 2 study to evaluate subcutaneous daratumumab in combination with standard multiple myeloma treatment regimens. The D-VRd cohort included adult subjects with newly diagnosed multiple myeloma, who were evaluated for clinical benefit in terms of very good partial response or better (VGPR) rate.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Information relating to orphan designation

Darzalex, was designated as an orphan medicinal EU/3/13/1153 on 17 July 2013. Darzalex was designated as an orphan medicinal product in the following indication:

- Treatment of plasma cell myeloma

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0264/2017 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	6 March 2024
Start of procedure:	30 March 2024
CHMP Rapporteur Assessment Report	6 June 2024
PRAC members comments	5 June 2024
Updated PRAC Rapporteur Assessment Report	6 June 2024
PRAC Outcome	13 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2024
Request for supplementary information (RSI)	27 June 2024
CHMP Rapporteur Assessment Report	19 August 2024
PRAC Rapporteur Assessment Report	20 August 2024
PRAC members comments	28 August 2024
Updated PRAC Rapporteur Assessment Report	Not applicable
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	13 September 2024
Opinion	19 September 2024

2. Scientific discussion

2.1. Problem statement

Disease or condition

Daratumumab is approved as monotherapy in subjects with relapsed and refractory multiple myeloma and in combination with standard of care regimens for transplant-ineligible and transplant-eligible newly diagnosed multiple myeloma and relapsed/refractory multiple myeloma.

The MAH submitted a variation application to extend the indication of daratumumab for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant in combination with bortezomib, lenalidomide and dexamethasone.

The proposed new indication is only for the subcutaneous use of daratumumab.

Epidemiology

Multiple myeloma, a malignant disorder of the plasma cells, is characterised by uncontrolled and progressive proliferation of a plasma cell clone and is estimated to represent 1.0% to 1.8% of all new cancer cases worldwide and approximately 10% of hematologic malignancies (Sung 2021; SEER 2022). In 2020, an estimated 176,404 patients were diagnosed with multiple myeloma globally, with a crude incidence rate of 2.3 cases per 100,000 persons and a world population age-standardized incidence rate of 1.8 cases per 100,000 persons (Ferlay 2020). In the EU-27 countries, the 2022 crude incidence rate was 7.9 cases per 100,000 persons, and the European population age-standardized incidence rate was 7.3 cases per 100,000 persons. The estimated number of new cases for the EU overall was 35,333 cases in 2022. In general, Western Europe had the highest incidence rates of multiple myeloma. Crude incidence rates ranged from 3.0 per 100,000 persons in Bulgaria to 11.3 per 100,000 persons in Denmark (European Cancer Information System 2023).

Despite the significant improvement in patients' survival in the recent decades, only 10%-15% of patients achieve expected survival compared with the matched general population (Usmani, Blood Cancer J. 2018)

The median age at diagnosis of MM is approximately 70 years (Palumbo 2011).

Biologic features and Clinical presentation

The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow hematopoietic precursors and overproduction of monoclonal proteins. Multiple myeloma is characterized by osteolytic lesions, usually in the pelvis, spine, ribs, and skull. Lesions are caused by expanding plasmacytomas or by cytokines secreted by myeloma cells that activate osteoclasts and suppress osteoblasts. Increased bone loss may also lead to hypercalcemia. Solitary extraosseous plasmacytomas are unusual but may occur in any tissue. In many patients, renal failure is present at diagnosis or develops during the course of the disorder and is caused by the deposition of light chains in the distal tubules or by hypercalcemia. Patients also often develop anaemia due to kidney disease or suppression of erythropoiesis by cancer cells. These signs and symptoms are commonly denoted by the mnemonic acronym CRAB: Calcemia, Renal damage, Anaemia, and Bone lesions (Palumbo 2011).

Management

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, aggressiveness of the disease, and related prognostic factors (Palumbo 2011). Patients with newly diagnosed multiple

myeloma (NDMM) are typically categorized into 2 subpopulations: Eligible for autologous stem cell transplant (ASCT) or transplant ineligible. Eligibility is usually defined by age and suitability for intensive treatment. Patients will typically receive an induction regimen followed by treatment with ASCT, followed by consolidation therapy and maintenance treatment. For those not considered eligible for ASCT, longer-term treatment with multiagent combinations, including alkylators (e.g., cyclophosphamide (C)) , steroids (e.g., dexamethasone (d)) and newer agents such as proteasome inhibitors (PIs) (e.g., bortezomib (V)) and immunomodulatory imide drug (IMiDs) (e.g., lenalidomide (R)) are currently considered standards of care.

Over the past decade, the introduction of new classes of drugs, such as PIs and IMiDs, have changed the management of frontline treatment in both transplant and nontransplant candidates (Kumar 2023 [NCCN Guidelines]; Durie 2017; Dimopoulos 2021 [ESMO Guidelines]; Cavo 2011; Palumbo 2014). Studies have indicated that multidrug combinations are superior to single- or double-agent combinations in treating multiple myeloma (Cavo 2012; van der Veer 2011).

Patients with NDMM who are eligible for ASCT

While multiple myeloma is primarily a disease of the elderly, approximately 37% of patients are <65 years (Palumbo 2011; Kyle 2003). For the majority of these younger patients, as well as selected, fit patients over the age of 65 years, an intensive treatment approach, including ASCT, is considered the standard of care according to both US (NCCN; Kumar 2023) and European guidelines (ESMO; Dimopoulos 2021; Gay 2018).

ASCT-eligible patients with NDMM generally receive an induction therapy and ASCT, sometimes followed by consolidation treatment and commonly followed by lenalidomide maintenance therapy.

Induction therapy in transplant-eligible patients.

VRd, along other triplet regimens such as VTd and VCd, is one of the preferred frontline regimens recommended by NCCN and ESMO treatment guidelines for the primary therapy of patients with NDMM who are transplant-candidates (Kumar 2023; Dimopoulos 2021). The recommendation is based upon randomized studies, including the IFM2009 and DETERMINATION studies, which demonstrated the benefit of ASCT and VRd compared with VRd alone in this patient population (Attal 2017; Richardson 2022). The randomized Phase 3 IFM2009 study established that three 21-day cycles of induction therapy with VRd, ASCT, 2 cycles of consolidation therapy, and 1 year of maintenance therapy with lenalidomide resulted in superior median PFS compared with 8 cycles of VRd and 1 year of maintenance with lenalidomide (47.3 vs 35.0 months). The subsequent DETERMINATION study, which had a similar study design but administered maintenance lenalidomide until PD, confirmed the benefit of ASCT with prolongation of median PFS (67.5 vs 46.2 months).

Daratumumab is approved in combination with VTd for the treatment of patients with NDMM who are eligible for ASCT (Moreau 2019). This regimen is listed as one of the options in the ESMO treatment guidelines for the treatment of patients who are transplant eligible.

High-dose chemotherapy and stem cell rescue

High-dose chemotherapy followed by ASCT is the standard approach for eligible patients, and recent Phase 3 trials have shown the benefit in the area of "novel agents" (Kumar 2018; Gay 2018; Attal 2017; Cavo 2016). After attaining an optimal response from induction therapy, blood stem cells are mobilized in peripheral blood with the use of G-CSF alone or with plerixafor in combination with G-CSF (Giralt 2009). Cyclophosphamide with G-CSF may be used in patients who are unable to mobilize with G-CSF alone. Stem cells are then harvested by apheresis/leukapheresis. High-dose chemotherapy typically consists of melphalan 140 to 200 mg/m2 followed 2 days later by infusion of previously collected autologous stem cells.

The autologous stem cells themselves have no therapeutic effect but decrease the duration of neutropenia and thrombocytopenia after high-dose chemotherapy reducing the risk of infectious and bleeding complications. The infusion of stem cells thus allows to increase the dose of chemotherapy administered with the hope to achieve a deeper remission and longer disease control.

Consolidation therapy in transplant-eligible patients

After transplant, some patients are given a further short intense period of treatment to deepen the response obtained with induction therapy, commonly referred to as consolidation therapy. Consolidation therapy administered after transplant generally has a short duration and aims to increase the depth of response after ASCT. Studies have demonstrated that consolidation therapy can enhance the depth of response achieved during previous treatment phases (Lee 2016). The VTd consolidation (2 cycles) improved response rates and PFS (Cavo 2012; Leleu 2013). Consolidation therapy with VTd yielded molecular remissions in up to 60% of patients (Ladetto 2010; Terragna 2010). Recently, a Phase 3 study (EMN02/HOVON95 MM TRIAL) showed an improvement of PFS with 2 cycles of a triplet consolidation therapy after ASCT (Sonneveld 2016; Sonneveld 2018). In general, the same triplet therapy that was used in induction is given as 2 cycles of treatment consolidation post transplantation.

Additionally, Study 54767414MMY3006 (CASSIOPEIA), a Phase 3 study, was the basis for the marketing authorization approval of daratumumab in combination with VTd in the first-line treatment of transplant-eligible patients with NDMM (Moreau 2019). In the first part of Study 54767414MMY3006, patients were randomized to receive induction and consolidation treatment with daratumumab in combination with VTd vs VTd alone. The data from Study 54767414MMY3006 demonstrated that D-VTd resulted in a clinical benefit that is both statistically significant and clinically meaningful compared with VTd alone. The improvement in depth of response achieved with D-VTd in this study was further supported by a statistically significant and clinically meaningful improvement in PFS, confirming deeper responses and superior long-term outcomes for participants who received D-VTd.

Maintenance therapy

Maintenance therapy is generally administered for a long duration and aims to improve PFS with minimal toxicity and without impacting quality of life. Lenalidomide was approved in the US and Europe in 2017 as monotherapy for maintenance therapy and is currently the standard of care. Lenalidomide is currently the only preferred maintenance therapy recommended by NCCN and ESMO guidelines.

2.1.1. About the product

Daratumumab is a human mAb that binds with high affinity to CD38, a transmembrane glycoprotein expressed on tumour cells, and induces tumour-cell death through multiple mechanisms of action. These mechanisms of action include several immune-mediated activities, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc γ receptor-mediated crosslinking of tumour-bound mAbs (Overdijk 2016).

2.1.2. The development programme, compliance with scientific advice

The MAH submitted a request for Scientific Advice for daratumumab on 01 September 2017. The objective of this Scientific Advice procedure was to seek CHMP input on the planned studies, MMY3014 and MMY3016 to evaluate daratumumab in combination with bortezomib, lenalidomide and dexamethasone (VRd) for the treatment of subjects with newly diagnosed multiple myeloma who are not receiving ASCT as part of initial therapy (MMY3016) and subjects with newly diagnosed multiple myeloma who are eligible for ASCT (MMY3014). The main discussion points with regards to Study MMY3014 were:

- Since the correlation between MRD and PFS has not yet been demonstrated the CHMP advised that it would be preferable for the MAH to seek regulatory approval with PFS as the primary endpoint, whilst MRD could be considered an intermediate endpoint.
- A re-randomisation strategy or alternatively a single maintenance treatment was suggested due to concerns on whether the study design (**Figure 4)** would allow evaluation of the correlation between MRD and PFS.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No environmental risk assessment for daratumumab was submitted, as daratumumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This application for an extension of the indication is mainly based upon the primary analysis results from the pivotal phase 3 study 54767414MMY3014 (PERSEUS, also referred to in this report as study MMY3014) further supported by the results from study 54767414MMY2004 (GRIFFIN, also referred to in this report as study MMY2004) and the D-VRd cohort of study 54767414MMY2040 (PLEIADES, also referred to in this report as study MMY2040). Clinical pharmacology objectives and endpoints were incorporated into the 3 clinical studies assessing daratumumab in combination with VRd.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number	Phase	Study Description/Design Participant Population	Study Drugs/Dose Regimen Number of Treated Participants

Study Number	Phase	Study Description/Design Participant Population	Study Drugs/Dose Regimen Number of Treated Participants
MMY3014	3	Randomized, open-label Participants with NDMM who are eligible for ASCT	Daratumumab (D-VRd arm only): SC 1800 mg QW for Cycles 1 to 2, Q2W for Cycles 3 to 6, and Q4W for Cycles 7+. Bortezomib: SC 1.3 mg/m^2 twice a week for Cycles 1 to 6. Lenalidomide: PO 25 mg daily on Days 1 to 21 for Cycles 1 to 6 and 10 mg daily on Days 1 to 28 for Cycles 7+ (15 mg starting at Cycle 10 unless there was a tolerability concern). Dexamethasone: PO 40 mg on Days 1 to 4 and 9 to 12 during Cycles 1 to 6. D-VRd treated = 351 VRd treated = 347
GRIFFIN	2	Randomized, open-label Participants with NDMM who were eligible for ASCT	Daratumumab (D-VRd arm only): IV 16 mg/kg QW for Cycles 1 to 4, Q3W for Cycles 5 and 6, and IV 16 mg/kg or SC 1800 mg Q4W or Q8W for Cycles 7+ for 24 months. Bortezomib: SC 1.3 mg/m^2 twice a week for 6 cycles or until end of Cycle 4, then for Cycles 5 and 6 at the same dose that was tolerated at the end of Cycle 4. Lenalidomide: PO 25 mg daily on Days 1 to 14 for Cycles 1 to 6 or until end of Cycle 4, then for Cycles 5 and 6 at the same dose that was tolerated at the end of Cycle 4., and 10 mg daily on Days 1 to 21 for Cycles 7+ (15 mg starting at Cycle 10 unless there was a tolerability concern). Dexamethasone: PO 40 mg QW for Cycles 1 to 6 or until end of Cycle 4, then for Cycles 5 and 6 at the same dose that was tolerated at the end of Cycle 4. For the D-VRd group, 20 mg administered as a pre-infusion medication replaced the oral dexamethasone dose for that day and 20 mg was administered as a pre-infusion medication for maintenance. D-VRd treated = 116 (16 in the safety run-in phase and 100 in the main study) VRd treated = 101

Study Number	Phase	Study Description/Design Participant Population	Study Drugs/Dose Regimen Number of Treated Participants
PLEIADES (D-VRd cohort)	2	Open-label Participants with NDMM who were eligible for ASCT	Daratumumab: SC 1800 mg on Days 1, 8, 15 for Cycles 1 to 3 and on Day 1 for Cycle 4. Bortezomib: SC 1.3 mg/m^2 on Days 1, 4, 8, and 11 for Cycles 1 to 4. Lenalidomide: PO 25 mg on Days 1 to 14 for Cycles 1 to 4. Dexamethasone: PO 20 mg on Days 1, 2, 8, 9, 15, 16 for Cycles 1 to 4.

2.3.2. Pharmacokinetics

Phase 3 Study MMY3014

Study Design

The randomised, open-label, multicentre, Phase 3 Study MMY3014 compared D-VRd to VRd in participants with NDMM who were eligible for ASCT. The treatment phase consisted of 28-day cycles, including 4 cycles of induction, followed by ASCT, then 2 cycles of consolidation, followed by maintenance therapy. Daratumumab SC 1800 mg was administered weekly on Days 1, 8, 15, and 22 for Cycles 1 to 2, then every 2 weeks on Days 1 and 15 for Cycles 3 to 6. For maintenance cycles 7 and over, participants received daratumumab SC every 4 weeks on Day 1 until documented disease progression or unacceptable toxicity.

For the D-VRd arm, serum samples were used to evaluate the pharmacokinetics of daratumumab and were collected predose on Day 1 of Cycles 1, 3, 5, 7, 9, and 12; predose on Day 15 of Cycle 4; on Day 4 of Cycles 1, 3, and 5; and at 8 weeks (±1 week) post-treatment.

Demographic and Baseline Characteristics

At the time of clinical cut-off (CCO) (01 August 2023), 351 participants in the D-VRd arm and 347 participants in the VRd arm received study treatment. Demographic and baseline disease characteristics were generally balanced between the 2 treatment arms. The median age was 60 years (range, 31-70 years). The median baseline body weight was 74.5 kg (range, 37.0-167.6 kg). The majority of the participants were white (92.1%), male (58.7%), and had an ECOG performance status of 0 (63.6%).

Serum Daratumumab Concentrations Over Time

The pharmacokinetic results from the D-VRd combination were consistent with observations following 1800 mg daratumumab SC administration in previous monotherapy and combination studies.

In Study MMY3014, the observed mean (SD) C_{max} of 115 (73.6) µg/mL following the first daratumumab SC administration occurred at Cycle 1 Day 4 and mean (SD) maximum C_{max} of 652 (244) µg/mL occurred at Cycle 3 Day 4 following weekly daratumumab SC administrations during induction treatment.

In Study MMY3014, mean maximum C_{max} at Cycle 3 Day 4 was 5.67-fold that of the C_{max} at Cycle 1 Day 4, indicating extensive systemic accumulation of serum daratumumab concentration following weekly daratumumab SC administrations during induction treatment.

The mean maximum C_{trough} of daratumumab, which occurred immediately prior to dose administration at Cycle 3 Day 1 predose, was similar across studies between participants treated with D-VRd (Study

MMY3014), daratumumab SC monotherapy, D-Pd, D-Rd, and D-Kd (526, 581, 537, 526, and 744 µg/mL, respectively).

The proportion of treated participants who proceeded to stem cell transplantation was similar between the treatment arms (D-VRd: 89.7%, VRd: 87.0%).

Phase 2 study GRIFFIN

Study Design

The randomised, multicentre, open-label, active-controlled Phase 2 Study GRIFFIN (MMY2004) compared D-VRd to VRd in participants with NDMM eligible for ASCT. A total of 116 participants were treated with D-VRd (16 in the safety run-in phase and 100 in the main study) and 101 participants were treated with VRd. Daratumumab IV 16 mg/kg was administered weekly during induction treatment (Days 1, 8, and 15 of Cycles 1-4), every 3 weeks during consolidation treatment (Day 1 of Cycles 5 and 6), and every 4 weeks or every 8 weeks during maintenance treatment (on Day 1 of Cycles 7 and over for 24 months). All induction and consolidation cycles were 21 days and maintenance treatment cycles were 28 days. After the implementation of protocol amendment 4, there was an option to administer daratumumab SC 1800 mg as maintenance treatment every 4 weeks or every 8 weeks (on Day 1 of Cycles 7 and over). Nineteen participants received at least 1 daratumumab SC injection, all during maintenance therapy.

Serum samples were used to evaluate the pharmacokinetic of daratumumab and were collected pre- and pos-tinfusion on Day 1 of Cycles 1, 4, 5, and 6, and at 4 weeks and 8 weeks post-treatment. Serum samples for evaluation of anti-daratumumab antibodies were collected pre-dose on Day 1 of Cycles 1, 4 and 5, and at 4 weeks and 8 weeks post-treatment.

Demographic and Baseline Characteristics

At the time of CCO (25 January 2019), all 16 participants in the safety run-in group received DVRd. In the main study, 201 participants received treatment (D-VRd: 100 participants; VRd: 101 participants). Additionally, 19 participants received at least 1 daratumumab SC injection, all during maintenance therapy.

Overall, demographics and baseline characteristics were balanced between the 2 randomized treatment groups. The majority of participants were male (118 [57.0%] participants) and white (161 [78.2%] participants). The median age was 60 years (range, 29-70 years) and the median baseline body weight was 82.0 kg (range, 37.4-158.6 kg). Approximately half of the participants (103 [50.7%]) had an ECOG score of 1 at baseline.

Serum Daratumumab Concentrations Over Time

The pharmacokinetic results from participants in the randomized D-VRd treatment group and participants in the safety run-in group were similar and consistent with observations from previous monotherapy and combination therapy following administration of daratumumab IV at the same dose regimen and schedule. The Cmax of daratumumab increased following weekly doses of daratumumab in Cycles 1 to 4. At Cycle 4 Day 1 post-infusion, the mean (SD) Cmax was 890 (236) µg/mL in participants in the randomized D-VRd treatment group, which was a 3.27-fold increase as compared with the value at Cycle 1 Day 1 post-infusion. Following less frequent dose administration of daratumumab (every 3 weeks) in Cycle 5, the Ctrough at Cycle 6 Day 1 pre-infusion and Cmax at Cycle 6 Day 1 post-infusion decreased to 129 (77.4) µg/mL and 461 (125) µg/mL, respectively, in the randomized D-VRd treatment group, compared with the values at Cycle 4 Day 1 post-weekly doses. Due to the long half-life of daratumumab, concentrations were quantifiable at 4 weeks and 8 weeks after the last dose of daratumumab. Intersubject variability for daratumumab exposure in the randomized D-VRd treatment group ranged from 26.6% to 31.8% CV in Cycles 1 to 6 for post-infusion concentrations and was 50.5% and 60.7% CV at 4 weeks and 8 weeks, respectively, after the last dose of daratumumab.

Phase 2 study PLEIADES (D-VRd cohort)

Study design

The randomised, multicenter, open-label Phase 2 Study PLEIADES (MMY2040) evaluated daratumumab SC in combination with VRd in participants with NDMM who were eligible for ASCT. A total of 67 participants were treated with D-VRd. In the D-VRd cohort, daratumumab SC 1800 mg was administered for Cycles 1 to 3 (on Days 1, 8, and 15) and for Cycle 4 (on Day 1).

Serum samples were collected predose on Day 1 of Cycles 1 and 3; postdose on Day 4 of Cycles 1 and 4; at EOT; and 8 weeks post-treatment and used to evaluate the pharmacokinetics of daratumumab. Serum samples for evaluation of anti-daratumumab antibodies and plasma samples for evaluation of anti-rHuPH20 antibodies were collected predose on Day 1 of Cycles 1 and 4, at EOT, and 8 weeks post-treatment.

Demographic and Baseline Characteristics

At the time of CCO (04 March 2019), 67 participants in the D-VRd cohort received study treatment. The median age of participants in the D-VRd cohort was 59 years. The majority of participants were male (71.6%). Most participants were white (56.7%) and the median baseline body weight was 77.0 kg (range, 43.0-147.6 kg). The majority of participants had an ECOG performance status of 0 to 1 (59.7% had an ECOG status of 0).

Serum Daratumumab Concentrations Over Time (D-VRd cohort)

The mean (SD) value for D-VRd Cmax after the first dose was 100 (48.5) µg/mL at Cycle 1 Day 4. The pharmacokinetic profile of daratumumab was consistent with previous data for the respective treatments (except for Cmax, which was lower with daratumumab SC administration compared with IV administration, as expected), and with daratumumab SC 1800 mg administration in other studies. The highest mean (SD) Ctrough of 635 (253) µg/mL was observed at the end of weekly dosage (after 9 weekly doses at Cycle 4 Day 1). At EOT, the mean (SD) serum daratumumab concentration was 414 (215) µg/mL. Due to the long half-life, concentrations of daratumumab were still detectable at 8 weeks after the last dose. The intersubject variability (%CV) for serum daratumumab concentrations ranged from 36.9% to 72.5% across all pharmacokinetic sampling timepoints.

Special populations

Weight

In the pharmacokinetic-evaluable population of Study MMY3014, the baseline body weight range was 44.5 to 125.0 kg, which was similar to that in other daratumumab SC studies. The body weight percentiles for Study MMY3014 (≤25%, >25% to ≤75%, and >75%) correspond to body weight categories of ≤66 kg, >66 to ≤86 kg, and >86 kg, respectively, which are similar to baseline body weight cutoffs used in this analysis.

In the study MMY3014, there was considerable overlap in serum daratumumab concentrations at pharmacokinetic sampling timepoints across body weight subgroups. However, consistent with a mAb administered SC by flat dose, higher serum daratumumab concentrations were observed in participants with lower body weight (≤65 and ≤50 kg) and lower serum daratumumab concentrations were observed in participants with higher body weight (>85 kg) at all pharmacokinetic sampling timepoints. For the lowest body weight subgroups (≤65 and ≤50 kg), mean Ctrough of daratumumab at Cycle 3 Day 1 predose was 17.5% and 63.1% higher, respectively, compared with that of the total pharmacokinetic-evaluable analysis set. For the highest body weight subgroup (>85 kg), mean Ctrough of daratumumab at Cycle 3 Day 1 predose was 11.6% lower compared with that of the total pharmacokinetic-evaluable analysis set. For the middle body weight subgroup (>65 to ≤85 kg and >50 to ≤85 kg), the mean concentration of daratumumab at Cycle 3 Day 1 predose was comparable to that of the total pharmacokinetic-evaluable analysis set. Five participants in the pharmacokinetic-evaluable analysis set had a body weight ≤50 kg and had mean (SD) daratumumab Cmax at Cycle 3 Day 4 of 1056 (223) µg/mL, which was within the range of Cmax (Cycle 3 Day 4) for participants in the total pharmacokinetic-

evaluable analysis set (0.957-1479 µg/mL). The flat-dose administration of daratumumab SC achieved adequate systemic exposure for all body weight subgroups in the D-VRd treatment arm (i.e., the systemic exposure in the majority of participants exceeded the 236 µg/mL threshold previously established to be necessary for 99% target saturation).

Race

In the MMY3014 study, the observed mean (SD) Ctrough,max of daratumumab at Cycle 3 Day 1 predose in black/African American participants (N=4) was 415 (154) µg/mL, approximately 21% lower than in white participants (526 [211] µg/mL, N=275). The observed mean (SD) Ctrough,max at Cycle 3 Day 1 predose in Asian participants (495 [90.3] µg/mL, N=4) appeared to be similar to that of white participants.

Pharmacokinetic interaction studies

Since there is no overlapping pathway of elimination, no interactions are expected between daratumumab and small-molecule drugs including VRd.

2.3.3. Pharmacodynamics

Pharmacodynamic/biomarker assessments were not conducted in Studies MMY3014, GRIFFIN, and PLEIADES, but the mechanism of action of daratumumab has been previously characterised.

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed on the surface of cells in a variety of haematological malignancies, including clonal plasma cells in multiple myeloma and AL amyloidosis, as well as other cell types and tissues. CD38 protein has multiple functions such as receptor mediated adhesion, signalling, and enzymatic activity.

Daratumumab has been shown to potently inhibit the in vivo growth of CD38-expressing tumour cells. Based on in vitro studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+Tregs) and B cells (CD38+Bregs) are decreased by daratumumab mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

Immunogenicity

The immune response-evaluable analysis set included participants who received at least 1 administration of daratumumab SC and had 1 or more ADA samples obtained after their first daratumumab SC administration. In the D-VRd treatment arm, 339 participants were included in the daratumumab immune response-evaluable analysis set and 338 participants were included in the rHuPH20 immune response-evaluable analysis set.

Incidence of Anti-daratumumab Antibodies

Two (0.6%) of the 339 participants in the daratumumab SC immune response-evaluable analysis set had treatment-emergent anti-daratumumab antibodies with peak titers of 1:48 and 1:192, respectively, indicating a low risk of immune response to daratumumab in combination with VRd. One of the 2 participants who tested positive for treatment-emergent anti-daratumumab antibodies was also positive for NAbs. In 1 of the 2 participants who was positive for anti-daratumumab antibodies, there was no apparent effect on the pharmacokinetics of daratumumab. Serum concentrations of daratumumab were lower in the other participant who was positive for treatment-emergent antibodies to daratumumab compared to participants who were negative for anti-daratumumab antibodies. However, these findings should be interpreted with caution given the small number of participants who tested positive for antibodies to daratumumab. Neither anti-daratumumab antibody-positive sample was associated with a systemic administration-related reaction (sARR).

Of note, 5 (1.5%) of the 339 participants in the daratumumab immune response-evaluable analysis set tested positive for anti-daratumumab antibodies at baseline (prior to receiving daratumumab SC treatment) with titers of 1:384 or lower. None of these participants were positive for treatment-emergent anti-daratumumab antibodies.

Incidence of Anti-rHuPH20 Antibodies

Twenty-one (6.2%) of the 338 participants in the recombinant human hyaluronidase PH20 (rHuPH20) immune response-evaluable analysis set tested positive for anti-rHuPH20 antibodies at baseline (prior to receiving daratumumab SC) with generally low titers data not shown).

Thirty-seven (10.9%) of the 338 participants in the rHuPH20 immune response-evaluable analysis set had treatment-emergent anti-rHuPH20 antibodies after the first daratumumab SC administration. Peak titers were generally low, and no participants had NAbs to rHuPH20. Daratumumab exposure was comparable between participants with and without treatment-emergent anti-rHuPH20 antibodies. These results were consistent with the reported incidence of treatment-emergent anti-rHuPH20 antibodies in previous daratumumab SC studies.

Efficacy exposure-response analysis

All participants from study MMY3014 who received at least one dose of daratumumab with at least one evaluable pharmacokinetic sample postdose (for the D-VRd arm) were included in the exposure-efficacy analysis.

The purpose of this analysis was to explore the E-R relationship to confirm and supplement the evidence of efficacy and safety of the daratumumab SC 1800 mg dose regimen in patients with NDMM.

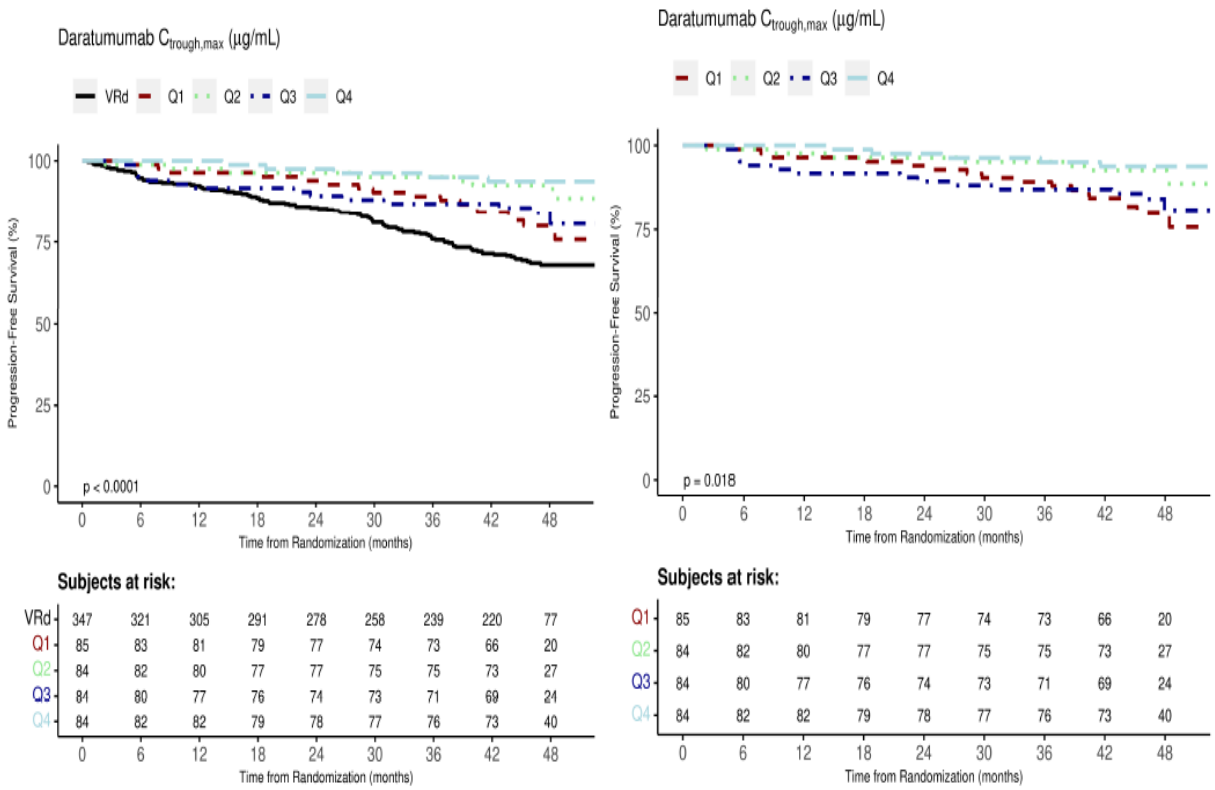
The relationship between exposure and the primary efficacy endpoint, PFS, was analysed graphically using Kaplan-Meier and Cox regression analysis. The effect of age, sex, body weight, race, renal and hepatic function, type of myeloma (IgG versus non-IgG), ISS, and ECOG status on efficacy was also evaluated.

Results

The intent-to-treat population included a total of 709 participants who were randomly assigned to D-VRd (N=355) or VRd (N=354) in a 1:1 ratio. Of the 709 participants, 11 participants did not receive any protocol-defined treatment (D-VRd: 4, VRd: 7) and 698 participants received at least 1 dose of study treatment (D-VRd: 351, VRd: 347). From the 351 participants assigned to the D-VRd arm, there were 14 participants who had missing pharmacokinetic exposure metrics (i.e., $C_{trough,max}$) for the exposure-efficacy analysis. Therefore, the efficacy dataset for the E-R analysis contained data from 684 participants (D-VRd: 337, VRd: 347).

The relationship between exposure and the primary efficacy endpoint, PFS, was analysed graphically using Kaplan-Meier and Cox regression analysis **(Figure 1**).

Figure 1. Kaplan-Meier Curves of Progression-free Survival by Daratumumab Exposure Subgroups in Combination with VRd in Study MMY3014

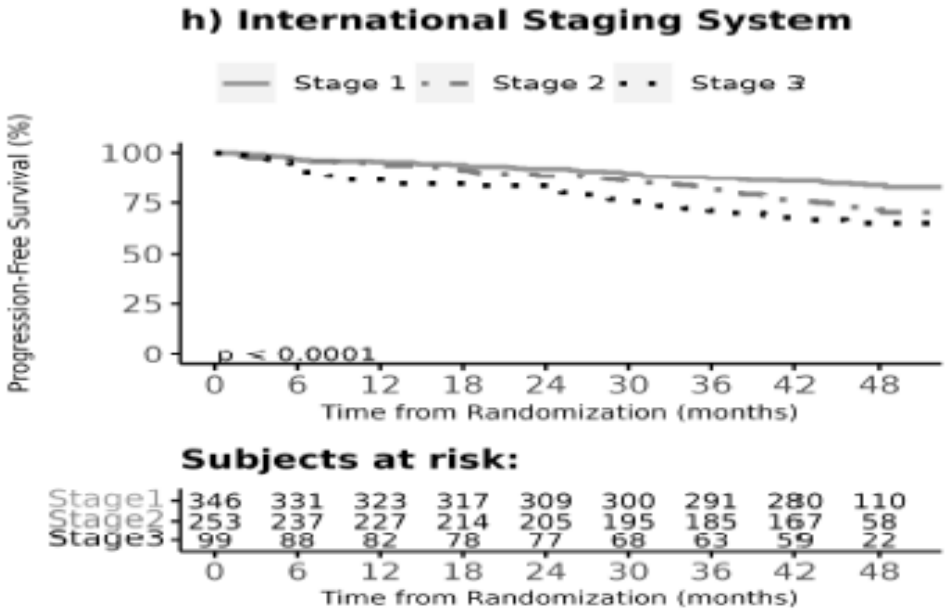


Most of the investigated covariates (i.e., age, sex, race, type of myeloma, renal and hepatic function) were well balanced between the VRd arm and the quartiles of exposure from the D-VRd arm.

Body weight and ISS showed imbalance across the quartiles of exposure in D-VRd. A slight trend for body weight (i.e., lower body weight in highest quartile Q4 and higher body weight in lowest quartile Q1) was observed among the quartiles of exposure The percentage of participants with ISS in stage 1 was lower in Q1 than the other 3 quartiles.

Because of the imbalanced covariates observed in the exposure quartiles, a covariate analysis for PFS was performed to determine the effect of demographic- and disease-related covariates on efficacy. As expected, the covariate that appeared to correlate with PFS was ISS (**Figure 2**).

Figure 2. Influence of the Covariates on Progression-free Survival: ISS



No differences in PFS were detected when the analysis was categorized into additional subgroups (i.e., sex or body weight tiers, age, ECOG status [0 versus 1 or above], type of myeloma [IgG versus non-IgG], hepatic function [normal versus impaired], renal function [≥90, 60 to 90, 30 to 60 mL/min], and race [non-white versus white]). Multivariate Cox regression analysis was conducted in a step-wise manner aiming to adjust the covariate effects of ISS and body weight. These covariates were not statistically significant and showed no exposure-effect modification when incorporated into the Cox regression model (data not shown).

Safety exposure-response analysis

All participants who received at least one dose of study treatment with at least one evaluable sample postdose were included in the exposure-safety analysis. The key safety endpoints of interest were included in the exposure-safety analysis.

The E-R relationship for safety was evaluated graphically by means of exploratory bar plots and direct comparison of TEAE rates across the exposure quartiles of daratumumab.

Results

The exposure-safety analysis for all selected TEAEs, was the same as that for the exposure-efficacy analysis, except for sARRs, which included 691 participants (D-VRd: 344, VRd: 347), as the relationship of sARRs was evaluated with $C_{peak,first}$, which was available from 344 participants who received D-VRd.

There was no apparent increase in TEAE rates with increasing exposure ($C_{peak,first}$ or $C_{peak,max}$) for sARRs, thrombocytopenia, anaemia, neutropenia, lymphopenia, or infections/infestations (all grades and Grades ≥3) within the studied drug concentration range in MMY3014 (data not shown).

2.3.4. PK modelling

Population PK (PPK) modelling

The PPK analysis was based on a total of 3889 daratumumab pharmacokinetic samples (3028 SC samples and 861 IV samples) from a total of 526 pharmacokinetic evaluable participants from Study MMY3014 (N=344; pharmacokinetic data cutoff date: 01 August 2023), GRIFFIN (N=115; pharmacokinetic data

cutoff date: 31 May 2022), and PLEIADES (N=67; pharmacokinetic data cutoff date: 07 December 2020). Pharmacokinetic evaluable participants were defined as participants who received at least 1 dose of daratumumab and had at least 1 measurable serum daratumumab concentration value above LLOQ after dose administration. The proportion of pharmacokinetic concentrations below the LLOQ of 0.2 µg/mL was low (1.6%).

At baseline, participants included in the PPK analysis had a median age of 60 years and median body weight of 77 kg (range, 43.0-158.6 kg). Of note, there were 7 participants with body weight <50 kg and 15 participants with body weight ≥120 kg. The analysis population was predominantly white race (65.6%) with normal renal function or mild renal impairment (73.2%), and normal hepatic function (71.3%). Disease characteristics included primarily low ECOG status (0 and 1: 93.4%), IgG myeloma (58.4%), and low ISS (49.6%). Statistics were generally similar across the different studies for most covariates, with no prominent differences in overall covariate distributions. Exceptions include a large proportion of participants from PLEIADES that were classified as "Other" race, and a considerable amount of missing data in GRIFFIN participants for hepatic/renal function as well as unevaluable or missing data for ADA status.

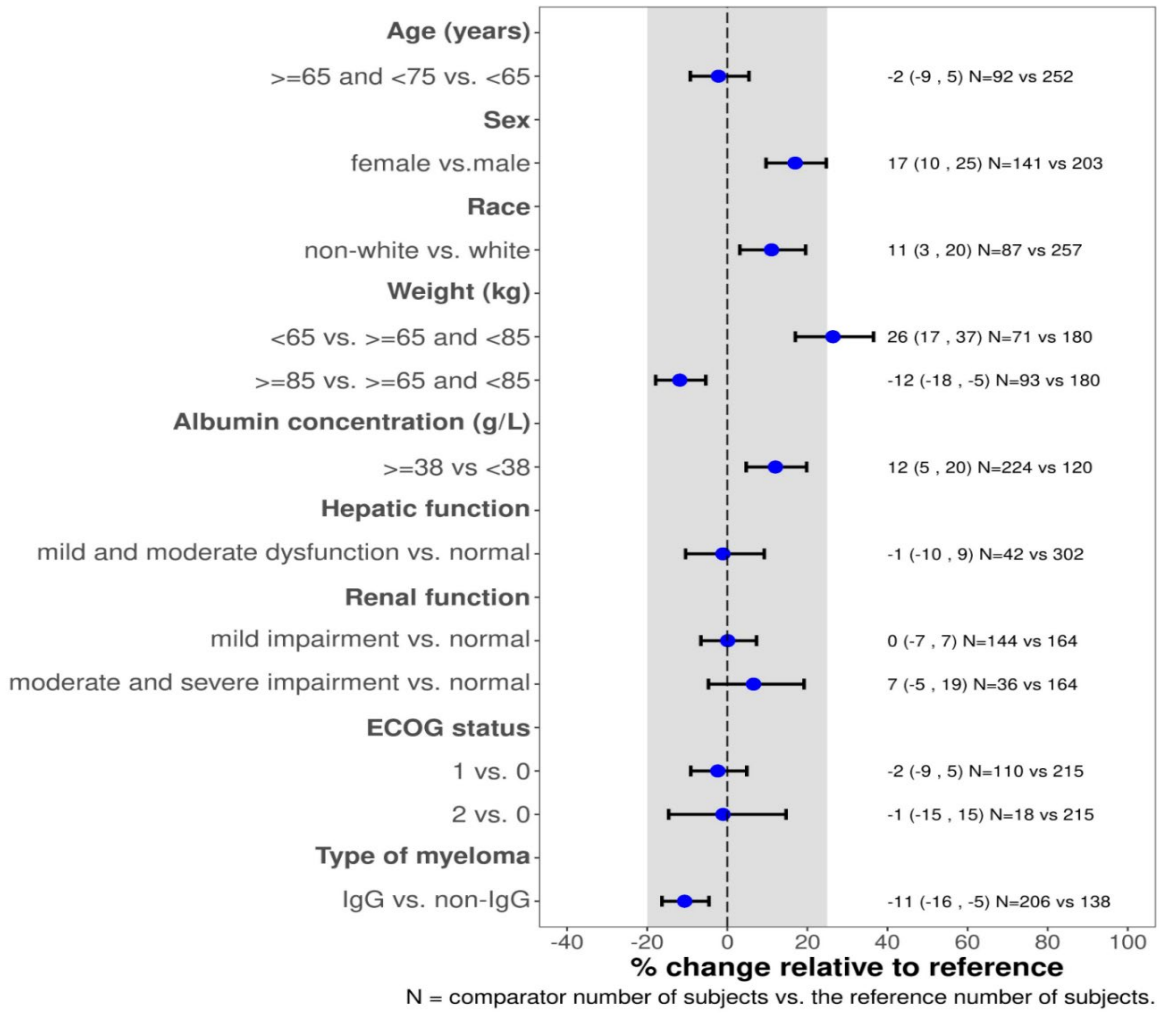
An external model evaluation was performed to verify the predictive performance of a previously developed PPK model with the current pooled clinical pharmacokinetic data which revealed a consistent underprediction of daratumumab concentrations relative to observed data. Based on the Goodness of Fir (GOF) plots and corresponding prediction-corrected visual predictive checks (pcVPC) results obtained from the external validation, the model parameters of the previously developed PPK model were re-estimated using a pooled dataset in Non-Linear Mixed Effects Model (NONMEM).

The observed concentration-time data of daratumumab were adequately described by a 2 compartment PPK model with parallel linear and nonlinear elimination pathways. The absorption of the daratumumab SC formulation was modeled as a first-order absorption process. Bioavailability (F1) was estimated to be 0.591, which is consistent with a previously developed IV/SC publication (Luo 2021; SC MM/Mod5.3.3.5/PPK Report) and other mAbs subcutaneously co-administered with rHuPH20 (Gibiansky 2021; Quartino 2016).

Daratumumab concentrations increased slowly after SC administration with a first-order absorption rate constant of 0.0176 1/h (0.422 1/day) and with Cmax typically reached approximately 5 to 7 days after first dose. Maximum Ctrough was reached at the end of the once-weekly dose schedule, ie, Cycle 3 Day 1, and maximum Cmax was reached at Cycle 3 Day 4 after the once-weekly dose schedule. The estimated linear CL (0.00429 L/h [0.103 L/day]) was somewhat lower than the reported CL of nonspecific endogenous IgG in the literature (Ryman 2017) and the V1 (6.71 L) was generally close to plasma volume; both parameters were related to body weight, as expected for mAbs. Linear CL, volumes of distribution, and absorption rate parameter estimates were similar to those previously reported (differences <30%) (Luo 2021; SC MM/Mod5.3.3.5/PPK Report).

A forest plot was created (**Figure 3**) for the comparison of daratumumab exposures in different subpopulations of interest including age, sex, race, body weight, albumin concentration, renal and hepatic function, ECOG status, and type of myeloma.

Figure 3. Forest Plot of Subgroup Analyses on Percent Change and 95% CI Relative to Reference Value for $C_{trough,C3D1}$ per the Recommended Dose Schedule for D-VRd Combination Therapy



Solid blue point represents percentage change of geometric mean and short horizontal bar represents 95% CI.
Dashed line represents reference value of zero.
Shaded area represents spans from -20 to +25 percentage change relative to reference.
Values represent percentage of change and the associated CI.

An additional evaluation was performed for weight groups ≤50 kg (N=5), >50 to ≤85 kg (reference, N=247), and >85 kg (N=92). The % change relative to reference (95% CI) was 62 (25, 109) for ≤50 kg vs >50 to ≤85 kg and -17 (-23, -11) for >85 kg vs >50 to ≤85 kg.

In the PPK analysis, race did not have a clinically meaningful effect on daratumumab pharmacokinetics.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

The PPK analysis included a total of 3889 daratumumab pharmacokinetic samples (3028 SC samples and 861 IV samples) from 526 pharmacokinetic-evaluable participants across three studies: MMY3014 (N=344), GRIFFIN (N=115), and PLEIADES (N=67). An external model evaluation was performed to verify the predictive performance of previously developed PPK model with the current pooled clinical

pharmacokinetic data. The previous PPK model was deemed unacceptable, and the parameters of the PPK model were re-estimated. After re-estimation of model parameters, the structure of the model remained the same as previously: daratumumab was described by a 2-compartment PPK model with parallel linear and nonlinear elimination pathways. Likewise, the covariate structure remained the same as previously with the effect of serum albumin concentration, body weight and type of myeloma (IgG versus non-IgG) on linear clearance; body weight and sex on volume of distribution in the central compartment, which is considered typical for mAbs. No significant bias was observed in any of the goodness-of-fit plots. The precision of estimated PK parameters was proved based on 95% CIs derived from standard errors from the covariance matrix and bootstrap analysis (830/1000). The shrinkage values suggested moderate to high shrinkage for most parameters, indicating potential challenges in estimating individual variability for CL, V1, Vmax, kdes, ka, and F1. The overall model performance was observed based on the study-stratified pcVPCs, suggesting no significant trends across the different percentiles.

The impact of covariates on the exposure metric Ctrough, C3D1 was evaluated using a forest plot. Forest plots with other exposure metrics were not presented. Immunogenicity was not evaluated in this subgroup analysis due to the small number of ADA-positive participants. The forest plot suggested that none of the investigated covariates (sex, race, body weight, albumin concentration, renal/hepatic function, ECOG status and type of myeloma) had clinically relevant effects on daratumumab pharmacokinetics, as expected from previous investigations. Based on these results, it seems that no additional dose recommendations are required for daratumumab.

Sparse PK-sampling was done in the 3 clinical studies which was conducted to support this application for use of daratumumab SC in combination with Lenalidomide, Bortezomib, and Dexamethasone (VRd) for treatment of NDMM in patients who are eligible for ASCT. The marketed drug product and SC dosing regimen of 1800 mg daratumumab was used in pivotal clinical study. In study MMY3014, daratumumab exposure was similar to that seen in monotherapy studies, with the maximum Ctrough (cycle 3 day 1 pre dose) mean ± SD of 526±209 µg/mL. Mean cycle 5 day 1 pre-dose concentration was considerably lower compared to study MMY3013. This difference was largely due to dosing interruption during the ASCT period. The pharmacokinetic profiles of daratumumab SC treatment of participants with NDMM who are eligible for ASCT were generally consistent with previous observations of daratumumab SC in combination and monotherapy studies.

The effect of covariates on PK, Ctrough at steady state, was evaluated from clinical PK-data in addition to the Pop-PK modelling.

The mean Cycle 3 Ctrough data showed as expected for a flat dosing regimen that the exposure was higher in the low BW groups, <50 kg and <65 kg, and that the exposure was lower in the high BW group, >85 kg. A comparable weight effect was observed in the Pop-PK analysis. The effect of weight on exposure is comparable to what was previously reported for Darzalex in the SmPC.

Pharmacodynamics

No exposure-response relationship for daratumumab has been demonstrated. A similar reduction in HR was found between exposure groups Q1 and Q3 and between Q2 and Q4. In all exposure quartiles a positive impact of adding daratumumab to VRd was demonstrated.

Body weight and ISS showed no exposure-effect modification on PFS in an adjusted model.

The immunogenicity results following daratumumab SC in combination with VRd treatment in participants with NDMM who were eligible for ASCT were consistent with observations in previous monotherapy and combination studies in multiple myeloma where development of anti-daratumumab antibodies was rare.

The exposure-safety relationship showed no apparent increase in TEAE rate with increasing daratumumab exposure for sARRs, thrombocytopenia, anaemia, neutropenia, lymphopenia, or infections.

2.3.6. Conclusions on clinical pharmacology

The provided pharmacokinetics data from 3 clinical studies the exposure-efficacy and exposure-safety analyses support the use of 1800 mg daratumumab SC in combination with VRd in patients with NDMM who are eligible for ASCT.

2.4. Clinical efficacy

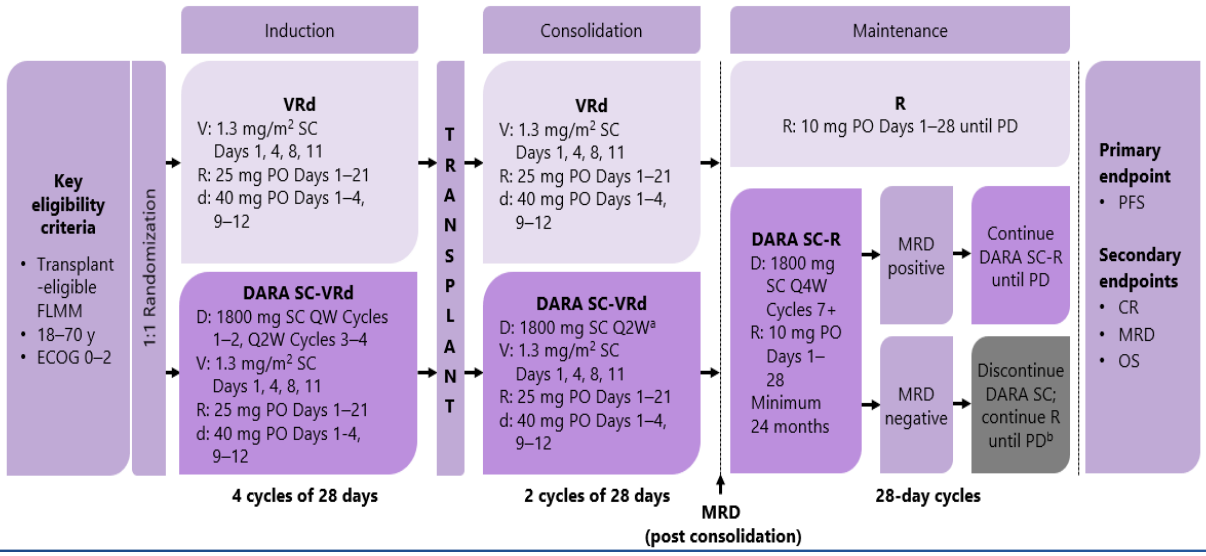
2.4.1. Main study

Study 54767414MMY3014 – PERSEUS: A phase 3 study comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) vs VELCADE, Lenalidomide, and Dexamethasone (VRd) in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy.

Methods

A diagrammatic representation of the study design is presented in **Figure 4**.

Figure 4. Study 54767414 / MMY3014 schematic



Study participants

Main inclusion criteria:

1. 18 to 70 years of age, inclusive.
2. Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the calcium, renal, anemia, bone (CRAB) criteria or biomarkers of malignancy criteria (SLiM-CRAB):
    a. CRAB criteria:

1. Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL)
2. Renal insufficiency: creatinine clearance <40mL/min or serum creatinine >177 µmol/L (>2 mg/dL)
3. Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL
4. Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT

b. Biomarkers of Malignancy (SLiM-CRAB):

1. Clonal bone marrow plasma cell percentage ≥60%
2. Involved: uninvolved serum free light chain ratio ≥100
3. >1 focal lesion on magnetic resonance imaging (MRI) studies

3. Measurable disease as defined by any of the following:
   a. Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
   b. Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio
4. Newly diagnosed subjects for whom high-dose therapy and autologous stem cell transplantation is part of the intended treatment plan.
5. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
6. Female subjects of child-bearing age should not be pregnant and avoid pregnancy

Main exclusion criteria:

1. Prior or current systemic therapy or SCT for any plasma cell dyscrasia, with the exception of emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.
2. Peripheral neuropathy or neuropathic pain Grade 2 or higher.
3. Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomization (exceptions are adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).
4. Radiation therapy for treatment of plasmacytoma within 14 days of randomization (palliative radiation for pain control secondary to lytic lesion is allowed within 14 days of randomization).
5. Plasmapheresis within 28 days of randomization.
6. Clinical signs of meningeal involvement of multiple myeloma.
7. Pulmonary:
   a. Subjects <65 years old with chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal.
   b. Subjects ≥65 years old with a FEV1 <50% or diffusing capacity of the lungs for carbon monoxide [DLCO] <50%.

8. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification. (subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

9. Any of the following:

    a. Known to be seropositive for human immunodeficiency virus (HIV).

    b. Seropositive for hepatitis B. Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time PCR measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded.

    c. Known to be seropositive for hepatitis C, (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

Treatments

Treatment Arm A (VRd):

- Bortezomib SC injection (1.3 mg/m^2) – D1, D4, D8, D11 during C1 to C6; induction: 4, 28-day cycles (C1 to C4); consolidation: 2, 28-day cycles (C5 to C6).
- Lenalidomide PO (25 mg) - D1 to D21 during C1 to C6; induction: C1-C4, 28-day cycles; consolidation: C5-C6, 28-day cycles.
    - Maintenance: 10 mg daily PO on D1 to D28 (continuously) of each 28-day cycle until PD or unacceptable toxicity.
- Dexamethasone PO (40 mg) on D1 to D4 and D9 to D12 of each 28-day cycle during induction/consolidation (C1 to C6)
- ASCT after 4 cycles of induction: Within 6 weeks after the completion of induction therapy (cycle 4), stem-cell mobilization was performed with the use of the local standard regimen, such as cyclophosphamide, granulocyte colony-stimulating factor, and plerixafor. A second round of stem-cell mobilization or bone marrow harvest was permitted if the stem-cell yield was considered by the investigator to be inadequate. Patients underwent conditioning with melphalan (200 mg per square meter of body-surface area) over a period of 24 to 48 hours, followed by autologous stem-cell transplantation. Consolidation therapy began 30 to 60 days after transplantation.

Treatment Arm B (D-VRd):

- VRd, ASCT and lenalidomide maintenance as described above.
- Daratumumab SC (1800 mg) – once every week for C1 to C2, then every 2 weeks for C3 to C6. For maintenance C7+, once every 4 weeks until PD or unacceptable toxicity. Participants with CR or better and sustained MRD-negativity for 12 months will stop daratumumab after a minimum of 24 months of maintenance therapy and restart if loss of CR without PD or loss of MRD-negativity.

Objectives

Primary

- To determine if the addition of daratumumab to VRd prolongs PFS compared with VRd alone

Secondary

- To determine if the addition of daratumumab to VRd will improve clinical outcome as measured by:

– Overall rate of CR or better

- Overall MRD-negativity rate achieved at any time during the study
- OS
- MRD-negativity rate post-consolidation
- ORR, rate of VGPR or better, rate of CR or better, and rate of sCR at post-induction, post-transplant, post-consolidation, and overall
- PFS2
- Time to response
- Duration of response
- To evaluate PROs and MRU
- To evaluate time to engraftment post-ASCT

Outcomes/endpoints

Primary

- Time from the date of randomisation to the date of disease progression (assessed by the International Myeloma Working Group (IMWG) 2011 criteria)

Secondary

- The percentage of ITT participants who achieved CR or sCR status anytime during the study per the 2011 IMWG criteria
- The proportion of ITT participants who achieved MRD-negativity (at or below the threshold of 10-5) by bone marrow aspirate and achieve CR or better response at any time after the date of randomization during the study (and prior to PD, subsequent therapy, or both).
- Measured from the date of randomization to the date the participant's death
- The proportion of ITT participants who achieve MRD-negativity (at or below the threshold of 10-5) at the end of consolidation and achieve CR or better response at any time of the study
- The proportions of ITT participants who achieved PR or better (VGPR or better, CR or better, or sCR) per 2011 IMWG criteria at post induction, post-transplant, post-consolidation, and overall
- The time from randomization to progression on next line of therapy or death, whichever comes first. PD on next line of treatment is based on investigator assessment.
- The time from randomization to date of initial PR or better response; time to CR/sCR defined as the time from randomization to date of initial CR/sCR
- The time from the date of first documentation of confirmed response (PR or better; CR or better) or first documentation of MRD negative status to the date of first documented evidence of PD, according to 2011 IMWG criteria, or death due to PD, whichever occurs first.
- Change in health-related quality of life, symptoms, and functioning using 2 EORTC questionnaires and the EQ-5D-5L
- ANC $\geq 0.5 \times 10^9$/L and platelet count $\geq 20 \times 10^9$/L

Sample size

The planned total sample size was approximately 690 participants. This was based on the assumptions that the median PFS for the VRd group would be 63 months and that the addition of daratumumab would decrease the risk of progression or death by 31% (HR=0.69; estimated median PFS of 91 months for D-VRd group). In order to achieve 85% power with a two-sided alpha of 0.05, 285 PFS events would be required. Assuming a 12-month accrual and 64-month of additional follow-up, approximately 690 subjects (345/arm) would be needed.

Long-term follow-up for survival will continue until approximately 310 deaths have been observed or 9 years have elapsed after the last subject is randomized, whichever occurs earlier. Per the protocol, this will provide approximately 70% power to detect a 25% reduction in the risk of death (HR=0.75) with a log-rank test at a 2-sided alpha of 0.05. However, a hazard ratio of 0.71 or less will provide at least 80% power. A large Phase 3 trial (CASSIOPEIA, MMY3006) comparing D-VTd versus VTd in a similar study population (N=1085), observed a HR of 0.66 from first randomization censoring the events from the crossover VTd subjects after Part 1 of the study with median follow-up of 18.8 months, such a HR would provide approximately 93.5% power for this study with 310 deaths.

Randomisation

This is a multi-centre randomised study. Participants are stratified by ISS Stage I, II, or III disease (β-2 microglobulin and albumin) and cytogenetics (standard-risk or high-risk as defined by presence of del17p, t[4;14] or t[14;16]) and then randomised in a 1:1 ratio.

Blinding (masking)

This is an open-label study.

Statistical methods

Analysis methods

For PFS, the primary analysis will consist of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment groups. The p-value from a stratified log-rank test will be reported. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect, measured by hazard ratio (Arm B vs. Arm A), and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include ISS staging (I, II, III), and cytogenetic risk (standard, high). The median PFS with 95% CI will be provided. The Kaplan-Meier PFS curve will also be plotted by treatment group.

In addition, PFS rates with 95% CI will be estimated by Kaplan-Meier method at landmarks (e.g., at 12-month, and 18-month, etc.) and reported for each treatment group. The number and percentage of subjects who had a PFS event or were censored will be reported. Reasons for PFS censoring will be summarized for ITT.

Sensitivity Analysis

The following sensitivity analyses will be conducted to evaluate the robustness of the primary analysis of PFS as appropriate.

Progressive Disease Based on Investigator Assessment: A sensitivity analysis of PFS, in which progressive disease is based on investigator assessment according to the IMWG response criteria. The PFS definition used in the sensitivity analysis is similar to that defined above, except for date of progressive disease and date of censoring. The date of progressive disease is the date of initial disease progression recorded in the Disease Progression CRF page or earliest date of confirmed progressive disease recorded in the Evaluation of Response CRF page, based on investigator assessment. Similarly,

the censoring date is the latest date of disease response recorded in the Evaluation of Response CRF page, based on investigator assessment. In addition, reasons for PFS and censoring based on investigator assessment will be summarized for ITT population.
Unstratified Analysis of PFS: A sensitivity analysis of PFS by using unstratified log-rank test and unstratified Cox's regression model will be performed in a similar manner as described for the primary analysis.

Not censored for Death/PD after Missing More Than One Disease Evaluation: A sensitivity analysis of PFS derived from the algorithm by not censoring for death or progression after missing consecutive evaluations will be performed in a similar manner as described for the primary analysis. For any PFS (death or progression) event identified by the computer algorithm, if there is more than one scheduled disease evaluation missed between the event date and the latest date of scheduled disease evaluation (includes serum M-protein, urine M-protein, and serum FLC only) immediately preceding the event, then this event will be considered as a PFS event in the analysis.

Key secondary Endpoint(s)

Overall CR or Better Rate

Overall CR or better rate is defined as the percentage of ITT subjects who achieved CR or sCR status anytime during the study per the IMWG criteria. In addition, the specific response must be achieved prior to start of subsequent therapies.

Overall MRD Negativity Rate

Overall MRD negativity rate is defined as the proportion of ITT subjects who achieve MRD negativity (at or below the threshold of 10-5) by bone marrow aspirate and achieve CR or better response at any time after the date of randomization during the study (and prior to progressive disease, subsequent therapy, or both). Subjects whose tested samples were found to be MRD positive or ambiguous, and subjects who were not tested will be considered as not achieving MRD negativity.

Overall Survival (OS)

OS is measured from the date of randomization to the date of death due to any cause. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subjects who died after consent withdrawal will be considered as having an OS event. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

Secondary time-to-event efficacy endpoints, including PFS2 and OS, will be analyzed using the same method as for PFS. For OS, the final analysis will occur after approximately 310 deaths have been observed. Earlier analyses, in which OS is analyzed, will be considered as interim analyses. Even if the significance of PFS has already been established, testing of OS will continue as planned until a definitive conclusion on OS is reached.

Comparison between the 2 treatment groups of response-related endpoints at different timepoints and other binary endpoints will be conducted using the stratified Cochran Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its two-sided 95% confidence interval, and will be provided as the measure of treatment effect. Time to and Duration of response (PR or better), CR/sCR, MRD negative status will be summarized descriptively without formal statistical comparison. A hierarchical testing will be used for the secondary efficacy endpoints to achieve strong control of the overall familywise Type I error rate at a two-sided significance level of 0.05.

Interim Analyses

The study design includes 2 interim analyses and a final analysis for PFS, the first interim analysis will be performed when approximately 143 PFS events have occurred (corresponds to 50% of the total planned PFS events), the second interim analysis for PFS will be performed when approximately 185 PFS events have occurred (corresponds to 65% of the total planned PFS). If the superiority of D-VRd over

VRd alone with respect to PFS could be established at the first or second interim analysis, the interim PFS analysis would serve as the primary PFS analysis, which otherwise is to occur when approximately 285 PFS events had been observed.

Only if the primary endpoint of PFS is statistically significant, the following key secondary endpoints would be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing the hierarchical testing approach that strongly controls Type I error rate. The key secondary endpoints will be tested in the following order:

1.Overall CR or better rate
2. Overall MRD negativity rate (threshold of 10-5)
3. Overall Survival
   - For Overall CR or better rate and MRD negativity rate (10-5) will only be tested at the interim or final PFS analysis when PFS is statistically significant.
   - For OS, descriptive analysis will be performed at the time of the first PFS interim analyses, expecting few OS events. In case PFS significance is established prior to the second interim or final PFS analysis, OS analysis will continue to be performed at approximately same time as if the second interim and final PFS analysis would occur (185, 285 PFS events). Expecting a long gap between the final PFS and final OS analysis, additional looks may be added to provide periodically OS updates until a definitive conclusion on OS is reached.

Futility Analysis of OS
All subjects in the ITT population were randomized between 19 January 2019 and 03 January 2020. Given that the study was fully enrolled and ongoing at the peak of the COVID-19 pandemic prior to the availability of vaccine and/or treatment, and multiple myeloma subjects with advance aged are at high risk of developing serious COVID-19 infection and resulting in death, no formal OS futility analysis will be conducted for this trial since it would be difficult to accurately assess COVID-19 impact on the OS, especially if there is any imbalance between the two arms. Instead, sensitivity OS analyses such as censoring the COVID-19 death shall be conducted at the planned analyses, together with the routine IDMC's cumulative safety data review (especially for COVID-19 cases, and exposure impacted by the pandemic) every 6 months before the primary PFS analysis. In the event that the observed OS HR is greater than 1, it would be more appropriate to put it in the context of safety profile and benefit-risk assessment.

Results

Participant flow

Patient disposition in study 54767414MMY3014 is summarised in

Table 1. Summary of Treatment Disposition; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd	Total
Analysis set: intent-to-treat	354	355	709
Subjects randomized but not treated[a]	7 (2.0%)	4 (1.1%)	11 (1.6%)
Subjects treated[a]	347 (98.0%)	351 (98.9%)	698 (98.4%)
Subjects who are still on treatment[b]	159 (45.8%)	260 (74.1%)	419 (60.0%)
Subjects who discontinued treatment[b]	188 (54.2%)	91 (25.9%)	279 (40.0%)
Reason for discontinuation[b]			
Adverse event	78 (22.5%)	32 (9.1%)	110 (15.8%)
COVID-19	1 (0.3%)	1 (0.3%)	2 (0.3%)
Progressive disease	72 (20.7%)	29 (8.3%)	101 (14.5%)
Subject refused further study treatment	14 (4.0%)	10 (2.8%)	24 (3.4%)
Death	11 (3.2%)	9 (2.6%)	20 (2.9%)
COVID-19	0	3 (0.9%)	3 (0.4%)
Physician decision	9 (2.6%)	8 (2.3%)	17 (2.4%)
Lost to follow-up	2 (0.6%)	3 (0.9%)	5 (0.7%)
Non-compliance with study drug	1 (0.3%)	0	1 (0.1%)
Other	1 (0.3%)	0	1 (0.1%)
COVID-19 related	0	0	0

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.
[a] Percentages are calculated based on the number of subjects randomized.
[b] Percentages are calculated based on the number of subjects treated.

At the CCO, 260 patients in the D-VRd arm remained on maintenance treatment (D-R) but of these 207 have discontinued daratumumab per protocol due to sustained MRD negativity. 159 patients remain on lenalidomide maintenance in the VRd arm. **Serum Daratumumab Concentrations Over Time**

Recruitment

Study Initiation Date: 03 January 2019 (first participant was screened).

Data Cutoff Date: 01 August 2023 (Last observation recorded as part of the database for interim analysis)

Conduct of the study

Summary of main protocol amendments

Amendment 1 (04 Sept 2018):

To add language describing hepatitis testing, which is now required across daratumumab studies for subjects who are positive for anti-HBc or anti-HBs.

Amendment 2 (09 April 2019):

The overall reason for the amendment is in response to identification of a new important risk (hepatitis B virus [HBV] reactivation). Additionally, revisions and clarifications were made to considerations for lenalidomide use, secondary endpoints, dosing, as well as other measurement parameters throughout the Protocol.

Amendment 3 (20 March 2020)

To remove language related to anticipated adverse events and align text with the daratumumab program standard language.

Amendment 4 (27 June 2022)

The key reasons for this protocol amendment are to align study visits with disease evaluation visits for both study arms, to include protocol text with respect to COVID-19 vaccines and guidance during the COVID-19 pandemic or another natural disaster, to update protocol text to align with EU CTR requirements including merging country-specific amendments into this Protocol Amendment 4, and to allow next-generation flow (NGF) in the Maintenance phase for determination of minimal residual disease (MRD) status to guide stopping/restarting of daratumumab.

Protocol deviations

A total of 46 (6.5%) participants had major protocol deviations, 20 (5.6%) participants in the D-VRd and 26 (7.3%) participants in the VRd arm (**Table 2**).

Table 2 . Summary of Subjects with Major Protocol Deviations; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd	Total
Analysis set: intent-to-treat	354	355	709
Subjects with major protocol deviations	26 (7.3%)	20 (5.6%)	46 (6.5%)
Received a disallowed concomitant treatment	15 (4.2%)	5 (1.4%)	20 (2.8%)
Entered but did not satisfy I/E criteria	4 (1.1%)	7 (2.0%)	11 (1.6%)
Received wrong treatment or incorrect dose	2 (0.6%)	8 (2.3%)	10 (1.4%)
Developed withdrawal criteria but not withdrawn	2 (0.6%)	0	2 (0.3%)
Other	4 (1.1%)	1 (0.3%)	5 (0.7%)

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

Note: Subjects may appear in more than one category.

Note: Percentages are calculated with the number of subjects in each group as denominator.

Baseline data

Table 3. Summary of demographics and baseline characteristics; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd	Total
Analysis set: intent-to-treat	354	355	709
Age, years			
N	354	355	709
Mean (SD)	58.1 (8.12)	58.7 (7.81)	58.4 (7.96)
Median	59.0	61.0	60.0
Range	(31; 70)	(32; 70)	(31; 70)
Category, n (%)			
< 50	54 (15.3%)	54 (15.2%)	108 (15.2%)
≥ 50 and < 65	213 (60.2%)	207 (58.3%)	420 (59.2%)
≥ 65	87 (24.6%)	94 (26.5%)	181 (25.5%)
Sex, n (%)			
N	354	355	709
Female	149 (42.1%)	144 (40.6%)	293 (41.3%)
Male	205 (57.9%)	211 (59.4%)	416 (58.7%)
Race, n (%)			
N	354	355	709
American Indian or Alaska Native	1 (0.3%)	2 (0.6%)	3 (0.4%)
Asian	6 (1.7%)	4 (1.1%)	10 (1.4%)
Black or African American	4 (1.1%)	5 (1.4%)	9 (1.3%)
Native Hawaiian or other Pacific Islander	2 (0.6%)	2 (0.6%)	4 (0.6%)
White	323 (91.2%)	330 (93.0%)	653 (92.1%)
Not Reported	18 (5.1%)	12 (3.4%)	30 (4.2%)
Ethnicity, n (%)			
N	354	355	709
Hispanic or Latino	20 (5.6%)	30 (8.5%)	50 (7.1%)
Not Hispanic or Latino	254 (71.8%)	242 (68.2%)	496 (70.0%)
Not Reported	80 (22.6%)	83 (23.4%)	163 (23.0%)
Weight[a], kg			
N	354	354	708
Mean (SD)	75.40 (17.314)	77.02 (14.932)	76.21 (16.176)
Median	73.00	75.40	74.50
Range	(37.0; 167.6)	(44.5; 125.0)	(37.0; 167.6)
Category, n (%)			
≤65	114 (32.2%)	82 (23.2%)	196 (27.7%)
>65 - 85	149 (42.1%)	175 (49.4%)	324 (45.8%)
>85	91 (25.7%)	97 (27.4%)	188 (26.6%)
Height, cm			
N	354	355	709
Mean (SD)	170.20 (10.416)	170.00 (9.525)	170.10 (9.973)
Median	170.00	170.00	170.00
Range	(145.0; 198.0)	(142.0; 195.0)	(142.0; 198.0)
BSA[a], m^2			
N	354	354	708
Mean (SD)	1.879 (0.2516)	1.901 (0.2193)	1.890 (0.2361)
Median	1.857	1.888	1.881
Range	(1.26; 2.80)	(1.37; 2.59)	(1.26; 2.80)
Baseline ECOG score[b], n (%)			
N	354	355	709
0	230 (65.0%)	221 (62.3%)	451 (63.6%)
1	108 (30.5%)	114 (32.1%)	222 (31.3%)
2	16 (4.5%)	19 (5.4%)	35 (4.9%)
3	0	1 (0.3%)	1 (0.1%)

VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

ECOG = Eastern Cooperative Oncology Group; BSA = Body Surface Area.

a One subject did not have baseline weight or BSA. The subject is randomized but not treated.

b One subject had ECOG 0 at randomization and worsened to ECOG 3 at baseline.

Note: Percentages are calculated with the number of subjects in each group with available data as denominator.

Table 4. Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd	Total
Analysis set: Intent-to-treat	354	355	709
Type of myeloma by immunofixation or serum FLC assay, n (%)			
N	354	355	709
IgG	200 (56.5%)	211 (59.4%)	411 (58.0%)
IgA	89 (25.1%)	76 (21.4%)	165 (23.3%)
IgM	0	2 (0.6%)	2 (0.3%)
IgD	5 (1.4%)	4 (1.1%)	9 (1.3%)
IgE	0	0	0
Light chain	49 (13.8%)	47 (13.2%)	96 (13.5%)
Kappa	32 (9.0%)	26 (7.3%)	58 (8.2%)
Lambda	15 (4.2%)	15 (4.2%)	30 (4.2%)
FLC-Kappa[a]	2 (0.6%)	5 (1.4%)	7 (1.0%)

Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd	Total
FLC-Lambda[b]	0	1 (0.3%)	1 (0.1%)
Biclonal	11 (3.1%)	15 (4.2%)	26 (3.7%)
Type of measurable disease[c], n(%)			
N	354	355	709
Serum	281 (79.4%)	282 (79.4%)	563 (79.4%)
IgG	185 (52.3%)	204 (57.5%)	389 (54.9%)
IgA	85 (24.0%)	65 (18.3%)	150 (21.2%)
Other[d]	11 (3.1%)	13 (3.7%)	24 (3.4%)
Urine only	46 (13.0%)	43 (12.1%)	89 (12.6%)
Serum FLC only	27 (7.6%)	29 (8.2%)	56 (7.9%)
NE[e]	0	1 (0.3%)	1 (0.1%)
Multiple myeloma diagnosis			
N	352	354	706
CRAB Criteria only[f]	113 (32.1%)	125 (35.3%)	238 (33.7%)
Biomarkers of malignancy only	65 (18.5%)	52 (14.7%)	117 (16.6%)
CRAB criteria and Biomarkers of malignancy (both)	174 (49.4%)	177 (50.0%)	351 (49.7%)
CRAB Criteria			
N	287	302	589
Hypercalcemia	31 (10.8%)	27 (8.9%)	58 (9.8%)
Renal insufficiency	8 (2.8%)	11 (3.6%)	19 (3.2%)
Anemia	129 (44.9%)	127 (42.1%)	256 (43.5%)
Bone lesions	237 (82.6%)	248 (82.1%)	485 (82.3%)
Biomarkers of Malignancy			
N	239	229	468
Clonal bone marrow plasma cell percentage >60%	122 (51.0%)	106 (46.3%)	228 (48.7%)
Involved: uninvolved serum FLC ratio >100	136 (56.9%)	113 (49.3%)	249 (53.2%)
>1 focal lesion on magnetic resonance imaging (MRI) studies	48 (20.1%)	66 (28.8%)	114 (24.4%)
ISS Staging[g], n(%)			
N	353	355	708
I	178 (50.4%)	186 (52.4%)	364 (51.4%)
II	125 (35.4%)	114 (32.1%)	239 (33.8%)
III	50 (14.2%)	55 (15.5%)	105 (14.8%)
IMWG Revised ISS staging[h], n(%)			
N	352	353	705
I	132 (37.5%)	132 (37.4%)	264 (37.4%)
II	203 (57.7%)	197 (55.8%)	400 (56.7%)
III	17 (4.8%)	24 (6.8%)	41 (5.8%)
Time from MM diagnosis to randomization (months)			
N	354	355	709
Mean (SD)	3.00 (11.414)	2.19 (4.459)	2.59 (8.664)
Median	1.12	1.18	1.15
Range	(0.1; 184.6)	(0.0; 46.5)	(0.0; 184.6)
Number of lytic bone lesions, n (%)			
N	354	355	709
None	114 (32.2%)	102 (28.7%)	216 (30.5%)
1-3	75 (21.2%)	84 (23.7%)	159 (22.4%)
4-10	74 (20.9%)	87 (24.5%)	161 (22.7%)
More than 10	91 (25.7%)	82 (23.1%)	173 (24.4%)
Presence of diffuse myeloma-related osteopenia, n (%)			
N	349	354	703

Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd	Total
Yes	76 (21.8%)	91 (25.7%)	167 (23.8%)
No	273 (78.2%)	263 (74.3%)	536 (76.2%)
Number of extramedullary plasmacytomas, n (%)			
N	354	355	709
0	338 (95.5%)	340 (95.8%)	678 (95.6%)
≥1	16 (4.5%)	15 (4.2%)	31 (4.4%)
% Plasma cells, bone marrow biopsy/aspirate, n (%)			
N	354	353	707
<10	14 (4.0%)	14 (4.0%)	28 (4.0%)
10-30	132 (37.3%)	138 (39.1%)	270 (38.2%)
>30	208 (58.8%)	201 (56.9%)	409 (57.9%)
% Plasma cells, bone marrow biopsy, n (%)			
N	159	158	317
<10	4 (2.5%)	8 (5.1%)	12 (3.8%)
10-30	50 (31.4%)	48 (30.4%)	98 (30.9%)
>30	105 (66.0%)	102 (64.6%)	207 (65.3%)
% Plasma cells, bone marrow aspirate, n (%)			
N	322	333	655
<10	28 (8.7%)	32 (9.6%)	60 (9.2%)
10-30	144 (44.7%)	148 (44.4%)	292 (44.6%)
>30	150 (46.6%)	153 (45.9%)	303 (46.3%)
Cytogenetic risk[i], n (%)			
N	354	355	709
Standard Risk	266 (75.1%)	264 (74.4%)	530 (74.8%)
High Risk[j]	78 (22.0%)	76 (21.4%)	154 (21.7%)
del(17p)	34 (9.6%)	36 (10.1%)	70 (9.9%)
t(4;14)	38 (10.7%)	33 (9.3%)	71 (10.0%)
t(14;16)	14 (4.0%)	11 (3.1%)	25 (3.5%)
Indeterminate	10 (2.8%)	15 (4.2%)	25 (3.5%)

VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; ECG = electrocardiogram; FLC = serum free light chain; ISS = International Staging System; MM = multiple myeloma; NE=not evaluable.

a - Includes subjects without a positive immunofixation but with evidence of free light chain kappa by FLC testing.

b - Includes subjects without a positive immunofixation but with evidence of free light chain lambda by FLC testing.

c - Includes subjects without measurable disease in serum and urine.

d - Includes subjects with IgD, IgM, IgE and biclonal.

e - One subject with no evaluable measurable disease.

f - At least one of the calcium, renal, anemia, bone (CRAB) criteria

g - ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

h - Determination is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4; 14), t(14; 16), or del17p by FISH/Karyotype testing and serum lactate dehydrogenase (LDH) at baseline.

i - Cytogenetic risk is based on FISH.

j - Subject may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)].

Note: Percentages are calculated with the number of subjects in each group with available data as denominator.

Numbers analysed

The number of participants included in each analysis set is provided

Table 5. Number of Subjects in Each Analysis Set; All Screened Subjects (Study 54767414MMY3014)

	VRd	D-VRd	Total
All screened subjects			824
Intent-to-treat analysis set	354	355	709
Per-protocol analysis set[a]	350	348	698
Safety analysis set[b]	347	351	698
Subject received maintenance treatment[c]	300	322	622
Pharmacokinetic analysis set[d]	-	349	349
Daratumumab Immunogenicity analysis set[d]	-	339	339
rHuPH20 Immunogenicity analysis set[d]	-	338	338

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.
[a] Includes subjects who are randomized and don't have major protocol deviation due to not meeting all entry criteria.
[b] Includes subjects who have received at least one dose of study treatment (partial or complete) in the study.
[c] Includes subjects who have received at least one dose of maintenance study treatment (partial or complete) in the maintenance phase.
[d] Includes subjects assigned to D-VRd group who have received at least 1 dose of daratumumab and have at least 1 sample value after the first administration of daratumumab.

Outcomes and estimation

Primary endpoint: Progression-free Survival

Table 6. Summary of Progression-free Survival Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 54767414MMY3014)

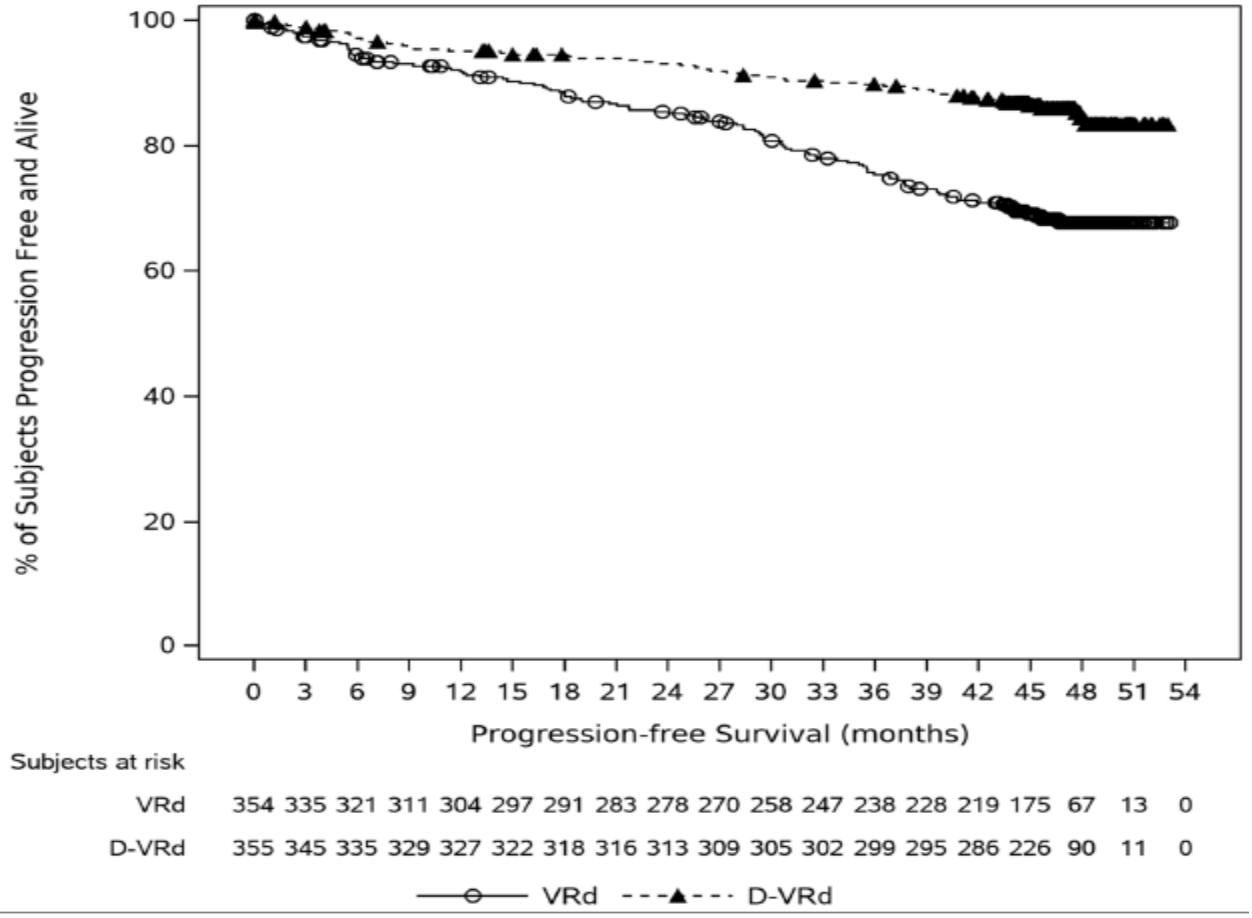
	VRd	D-VRd
Analysis set: intent-to-treat	354	355
Progression-free survival (PFS)		
Number of events (%)	103 (29.1%)	50 (14.1%)
Number of censored (%)	251 (70.9%)	305 (85.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	36.86 (30.85, 43.66)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.42 (0.30, 0.59)
6-month PFS rate % (95% CI)	94.5 (91.5, 96.4)	97.1 (94.7, 98.4)
12-month PFS rate % (95% CI)	91.8 (88.3, 94.3)	95.1 (92.2, 96.9)
24-month PFS rate % (95% CI)	85.4 (81.1, 88.8)	93.0 (89.8, 95.3)
36-month PFS rate % (95% CI)	75.4 (70.3, 79.7)	89.7 (86.0, 92.5)
48-month PFS rate % (95% CI)	67.7 (62.2, 72.6)	84.3 (79.5, 88.1)
60-month PFS rate % (95% CI)	NE (NE, NE)	NE (NE, NE)

VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; CI = confidence interval; NE = not evaluable.

a - p-value is based on the log-rank test stratified with ISS staging (I, II, vs. III), and cytogenetic risk (high risk vs. standard risk or unknown).

b - Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, vs. III), and cytogenetic risk (high risk vs. standard risk or unknown). A hazard ratio <1 indicates an advantage for D-VRd.

Figure 5. Kaplan-Meier Plot for Progression-free Survival Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 54767414MMY3014)



VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone

Data from 85.9% of participants in the D-VRd arm and 70.9% of participants in the VRd arm were censored at the time of this CCO. The majority of these participants were censored due to clinical cutoff (D-VRd: 286/355 [80.6%]; VRd: 215/354 [60.7%]).

Secondary endpoint: Overall CR or better Rate

This endpoint was defined as "*the percentage of ITT participants who achieved CR or sCR status anytime during the study per the 2011 IMWG criteria".*

Table 7. Summary of Overall Response Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd		D-VRd		Odds Ratio (95% CI)[a]	P-value[b]
	n(%)	95% CI for %	n(%)	95% CI for %		
Analysis set: intent-to-treat	354		355			
Response category						
Stringent complete response (sCR)	158 (44.6%)	(39.4%, 50.0%)	246 (69.3%)	(64.2%, 74.1%)	2.83 (2.08, 3.86)	<0.0001
Complete response (CR)	90 (25.4%)	(21.0%, 30.3%)	66 (18.6%)	(14.7%, 23.0%)		
Very good partial response (VGPR)	68 (19.2%)	(15.2%, 23.7%)	26 (7.3%)	(4.8%, 10.5%)		
Partial response (PR)	16 (4.5%)	(2.6%, 7.2%)	5 (1.4%)	(0.5%, 3.3%)		
Stable disease (SD)	9 (2.5%)	(1.2%, 4.8%)	4 (1.1%)	(0.3%, 2.9%)		
Progressive disease (PD)	1 (0.3%)	(0.0%, 1.6%)	2 (0.6%)	(0.1%, 2.0%)		
Not evaluable (NE)	12 (3.4%)	(1.8%, 5.8%)	6 (1.7%)	(0.6%, 3.6%)		
CR or better (sCR + CR)	248 (70.1%)	(65.0%, 74.8%)	312 (87.9%)	(84.0%, 91.1%)	3.13 (2.11, 4.65)	<0.0001
VGPR or better (sCR + CR + VGPR)	316 (89.3%)	(85.6%, 92.3%)	338 (95.2%)	(92.4%, 97.2%)	2.40 (1.33, 4.35)	0.0029
Overall response (sCR+CR+VGPR+PR)	332 (93.8%)	(90.7%, 96.1%)	343 (96.6%)	(94.2%, 98.2%)	1.89 (0.92, 3.87)	0.0762

VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; Dara = daratumumab; Bor = bortezomib; Len = lenalidomide, Dex = dexamethasone or equivalent; CI = confidence interval.

a - Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, vs. III) and cytogenetic risk (high risk vs. standard risk).

b - P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations. Percentages are calculated with the number of subjects in each group as denominator.

Improvements were observed in the D-VRd arm compared with the VRd arm for VGPR or better but not CR or better rates at the end of induction and at the end of ASCT, and for VGPR or better, CR or better, and sCR rates at the end of consolidation (data not shown). Overall, absolute differences between treatment arms increased through treatment phases for CR or better rates favouring the D-VRd arm.

Secondary endpoint: Overall MRD-Negativity Rate

Overall MRD-negativity rate was defined as the proportion of participants in the ITT population who achieved both MRD-negativity by NGS per clonoSEQ test (at or below a sensitivity threshold of 10^{-5}) in bone marrow aspirate and a CR or better response at any time after the date of randomization (and prior to disease progression, receipt of subsequent therapy, or both).

Participants whose tested samples were found to be MRD-positive or ambiguous, and participants who were not tested were considered as not achieving MRD-negativity.

Table 8. Summary of Overall MRD Negativity Rate by NGS at or below 10^{-5} in Participants with CR or Better; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd
Analysis set: intent-to-treat	354	355
MRD Negativity Rate (at or below 10^{-5})	168 (47.5%)	267 (75.2%)
95% CI[a] of MRD negativity rate	(42.2%, 52.8%)	(70.4%, 79.6%)
Odds ratio with 95% CI[b]		3.40 (2.47, 4.69)
P-value[c]		<0.0001

MRD = minimal residual disease.; VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

a Exact 95% confidence interval.

b Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, vs. III) and cytogenetic risk (high risk vs. standard risk).

c P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

Note: Percentages are calculated with the number of subjects in each group as denominator.

Other MRD-related Analyses

Overall MRD-negativity Rate at 10^{-6} Threshold

Table 9. Summary of Overall MRD Negativity Rate by NGS at 10^{-6} in Participants with CR or Better; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd
Analysis set: intent-to-treat	354	355
MRD Negativity Rate (at or below 10^{-6})	114 (32.2%)	231 (65.1%)
95% CI[a] of MRD negativity rate	(27.4%, 37.3%)	(59.9%, 70.0%)
Odds ratio with 95% CI[b]		3.97 (2.90, 5.43)
P-value[c]		<0.0001

MRD = minimal residual disease; VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

a - Exact 95% confidence interval.

b - Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, vs. III) and cytogenetic risk (high risk vs. standard risk).

c - P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

Note: Percentages are calculated with the number of subjects in each group as denominator.

MRD-Negativity Rate Post-consolidation

Table 10. Summary of Overall MRD Negativity Rate by NGS at or below 10^{-5} in Participants with CR or Better by the End of Consolidation Phase; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd
Analysis set: intent-to-treat	354	355
MRD Negativity Rate (at or below 10^{-5})	115 (32.5%)	204 (57.5%)
95% CI[a] of MRD negativity rate	(27.6%, 37.6%)	(52.1%, 62.7%)
Odds ratio with 95% CI[b]		2.79 (2.06, 3.78)
P-value[c]		<0.0001

MRD = minimal residual disease; VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

a Exact 95% confidence interval.

b Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, vs. III) and cytogenetic risk (high risk vs. standard risk).

c P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

Note: Percentages are calculated with the number of subjects in each group as denominator.

Sustained MRD-negativity Rate

Sustained MRD-negativity was defined as 2 consecutive MRD-negative results (at or below 10^{-5}) at least 12 months apart, without any MRD-positive (10^{-4} or higher) results in between.

Table 11. Summary of Sustained MRD-Negativity Rate by NGS at or below 10^{-5} in Participants with CR or Better; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd
Analysis set: intent-to-treat	354	355
Sustained MRD-negativity rate (10^{-5})[a]	105 (29.7%)	230 (64.8%)
95% CI[b] of Sustained MRD-negativity rate	(24.9%, 34.7%)	(59.6%, 69.8%)
Odds ratio with 95% CI[c]		4.42 (3.22, 6.08)
P-value[d]		<0.0001

MRD = minimal residual disease; VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

a Sustained MRD-negativity is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between.

b Exact 95% confidence interval.

c Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, vs. III) and cytogenetic risk (high risk vs. standard risk).

d P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.

Secondary endpoint: Overall survival

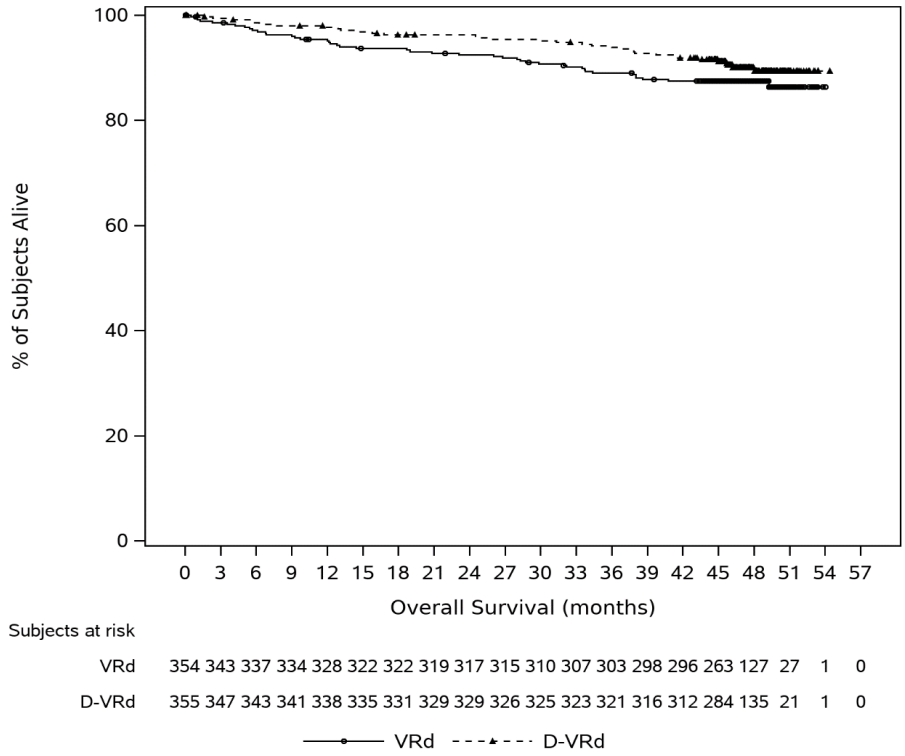
Table 12. Summary of Overall Survival; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd
Analysis set: intent-to-treat	354	355
Overall Survival		
Number of events (%)	44 (12.4%)	34 (9.6%)
Number of censored (%)	310 (87.6%)	321 (90.4%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI) [a]		0.73 (0.47, 1.14)
12-month survival rate % (95% CI)	95.1 (92.2, 96.9)	97.7 (95.5, 98.8)
24-month survival rate % (95% CI)	92.5 (89.2, 94.8)	96.3 (93.6, 97.8)
36-month survival rate % (95% CI)	89.0 (85.2, 91.9)	94.2 (91.2, 96.2)
48-month survival rate % (95% CI)	87.5 (83.5, 90.6)	89.4 (85.4, 92.4)
60-month survival rate % (95% CI)	NE (NE, NE)	NE (NE, NE)

VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; CI = confidence interval; NE = not evaluable.

a - Hazard ratio from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), and cytogenetic risk (high risk vs. standard risk or unknown). A hazard ratio < 1 indicates an advantage for D-VRd.

Figure 6. Kaplan-Meier Plot for Overall Survival; Intent-to-treat Analysis Set (Study 54767414MMY3014)



VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

Progression-free Survival on Next Line of Therapy

At the time of the CCO, only 42 (11.8%) participants in the D-VRd arm and 58 (16.4%) in the VRd arm had had a PFS2 event. Analysis of PFS2 demonstrated a difference for participants treated with D-VRd with a HR=0.68 (95% CI: 0.46, 1.01; nominal 2-sided p=0.0529) compared with VRd treatment suggesting a longer PFS2 for patients randomised to the D-VRd arm.

Time to subsequent anti-myeloma therapy

Consistent with the improved PFS observed in the D-VRd arm, the time to subsequent antimyeloma therapy was longer for participants in the D-VRd arm compared with VRd arm (HR=0.31, 95% CI: 0.21, 0.46; nominal 2-sided p-value <0.0001). The median time to subsequent anti-myeloma therapy was not reached in either treatment arm.

Subsequent Therapies

Fewer participants in the D-VRd arm (33 [9.4%]) received subsequent anti-myeloma therapies compared with the VRd arm (93 [26.8%]). Of the participants receiving subsequent therapies (D-VRd: 33 participants; VRd: 93 participants), the most common (≥10%) subsequent antineoplastic drugs were:

- carfilzomib (D-VRd: 69.7%; VRd: 46.2%)
- bortezomib (D-VRd: 27.3%; VRd: 30.1%)
- cisplatin (D-VRd: 12.1%; VRd: 4.3%)
- daratumumab (D-VRd: 18.2%; VRd: 66.7%)

- isatuximab (D-VRd: 9.1%; VRd: 10.8%)
- belantamab mafodotin (D-VRd: 18.2%; VRd: 5.4%)
- teclistamab (D-VRd: 12.1%; VRd: 6.5%)
- cyclophosphamide (D-VRd: 36.4%; VRd: 23.7%)
- melphalan (D-VRd: 27.3%; VRd: 15.1%)
- doxorubicin (D-VRd: 18.2%; VRd: 7.5%)
- etoposide (D-VRd: 15.2%; VRd: 5.4%)
- dexamethasone (D-VRd: 84.8%; VRd: 83.9%)
- pomalidomide (D-VRd: 42.4%; VRd: 31.2%)
- lenalidomide (D-VRd: 24.2%; VRd: 25.8%)

Subsequent ASCT was reported for 10 (2.8%) participants in the D-VRd arm and 15 (4.3%) participants in the VRd arm.

Stem cell-related procedures, transplant and time to engraftment

Only time to engraftment post-ASCT was a predefined secondary endpoint but other aspects related to stem-cell procedures such as mobilization, harvesting, and conditioning can also be considered part of both the efficacy and safety assessment of D-VRd vs. VRd.

The number of CD34+ stem cells collected was lower in the D-VRd arm (Median: D-VRd: 5.52x106/kg; VRd: 7.435 x106/kg) despite higher usage of plerixafor.

More participants undergoing mobilization in the D-VRd arm (40%, 134/351) received plerixafor than in the VRd arm (22.7%, 72/347).

A higher number of patients failed stem cell mobilization in the D-VRd arm (9 vs 3) suggesting that daratumumab can reduce the probability for a successful stem cell harvest. However, the frequency of patients who made it to successful engraftment post ASCT based on the ITT population was higher in the D-VRd arm compared to the VRd arm with 88.5% (314/355) vs 84.7% (300/354) respectively.

The proportion of participants proceeding to autologous stem cell transplant did not differ between study arms. 89.7% (315/351) of patients in the D-VRd arm proceeded to transplant. 87.0% (302/347) of patients in the VRd arm proceeded to transplant.

One participant in the VRd arm died after melphalan conditioning therapy due to an adverse event and as such did not receive stem cell infusion.

Despite increased use of plerixafor for stem cell mobilization and lower amount of collected CD34+ stem cells in the D-VRd arm, the following was observed: Similar rates of hematopoietic reconstitution were observed among transplanted participants for both treatment arms (D-VRd: 99.7% (314/315); VRd: 99.3% (300/302)). Median time to engraftment was similar between the two arms (D-VRd: 15.7 days ; VRd: 14.9 days).

Three participants died following stem cell infusion but before engraftment, 1 participant in the D-VRd arm (due to post procedural sepsis) and 2 participants in the VRd arm (1 due to sepsis and 1 due to pneumonia influenza).

Patient reported outcomes

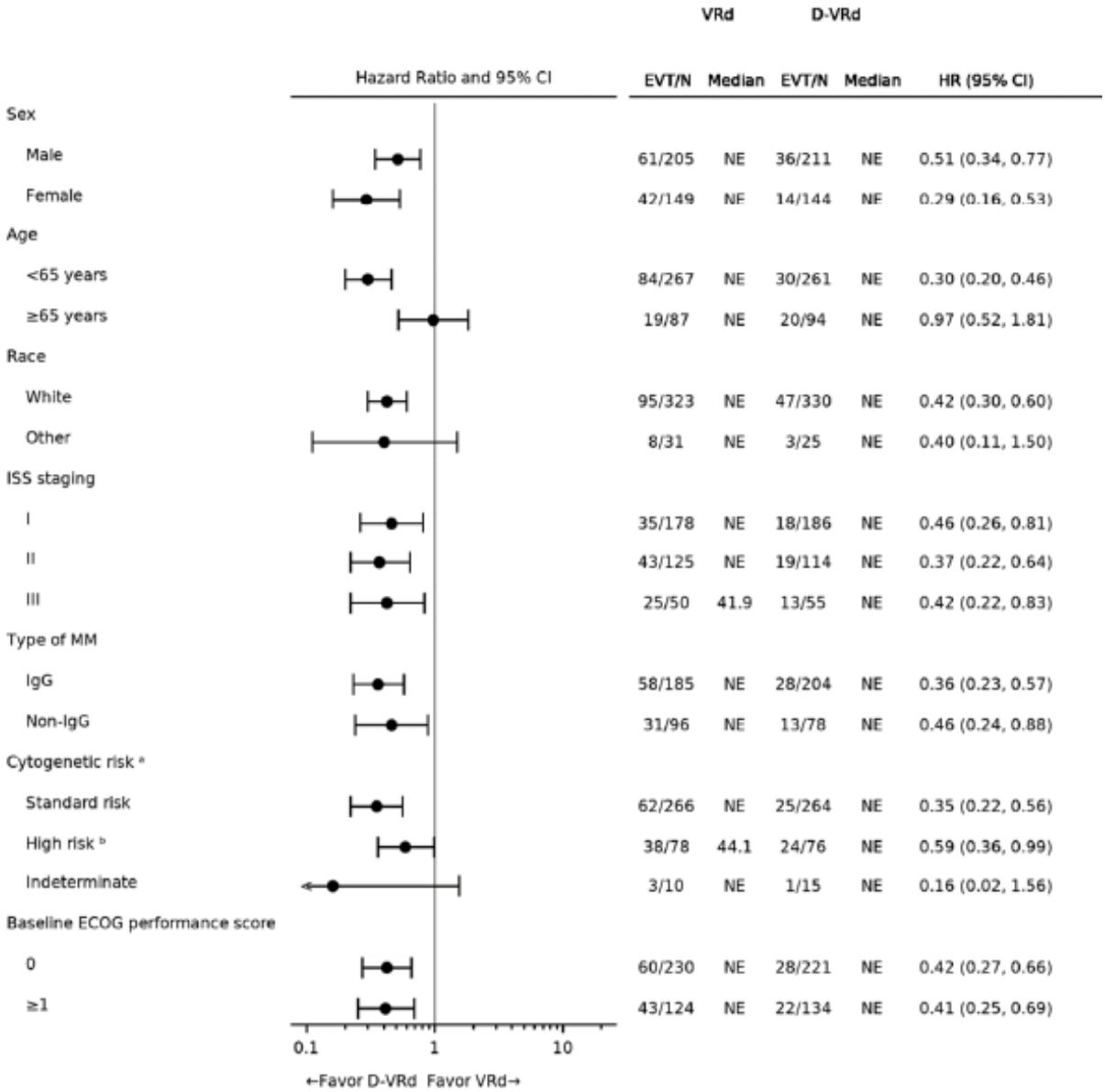
Patient reported outcomes (PROs) were measured by EORTC QLQ-C30 and EORTC QLQ-MY20 scale scores and EQ-5D-5L. The compliance rate for PRO assessments was high and comparable between both treatment arms.

Across all inventories consistent and comparable improvements in both arms were observed.

Ancillary analyses

Subgroup Analyses of Progression-free Survival

Table 13. Forest Plot of Subgroup Analyses on Progression-free Survival Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 54767414MMY3014)



VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; CI = confidence interval; EVT = Number of subjects with an event in each subgroup; N = Number of subjects in the intent-to-treat analysis set with data in each subgroup; HR = Hazard Ratio.

a - Cytogenetic risk is based on FISH.

b - Subject may have more than one high-risk abnormality [del17p, t(4;14) or t(14;16)].

Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio <1 indicates an advantage for D-VRd.

Efficacy in the ≥65 years Subgroup

The subgroup of participants age ≥65 years represents approximately 25% of the study population in the primary analysis, 181 participants of 709 total (D-VRd: 94 participants; VRd: 87 participants).

The primary analysis of PFS used the stratified analysis accounting for any differences in the 2 prognostic factors of cytogenetic risk and ISS stage. In contrast, the pre-planned subgroup analyses were based on the unstratified analysis to avoid inadequate number of participants in any given stratum within a specific subgroup. This analysis together with a number of post-hoc analysis stratified by various baseline disease characteristics are summarised in **Table 14**.

Table 14. Progression-free Survival Analyses for the ≥65 years Subgroup

Progression-free survival (PFS)	Age ≥65 years	
	D-VRd (n=94)	VRd (n=87)
	Hazard ratio (95% CI)	
Univariate analysis [a] Primary censoring rules Not censored the events after 2 missing consecutive disease evaluation	 0.97 (0.52, 1.81) 0.83 (0.45, 1.52)	
Stratified by cytogenetic risk and ISS staging [b] Primary censoring rules Not censored the events after 2 missing consecutive disease evaluations	 0.74 (0.39, 1.43) 0.67 (0.36, 1.26)	
Multivariate Analysis (cytogenetic risk, ISS staging, sex and baseline ECOG performance score) [c] Primary censoring rules Not censored the events after 2 missing consecutive disease evaluations	 0.80 (0.41, 1.54) 0.72 (0.38, 1.36)	

a - Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable

b - Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, vs. III), and cytogenetic risk (high risk vs. standard risk or unknown)

c - Hazard ratio and 95% CI from a Cox proportional hazards model with important baseline covariates identified by the stepwise model selection procedure, including treatment (D-VRd or VRd), cytogenetic risk (high risk vs. standard risk or unknown), ISS staging (I, II, vs. III), sex (male or female), and ECOG (0, or ≥ 1) as the explanatory variables

Key secondary efficacy endpoints CR and overall MRD-negativity

The results of the secondary endpoints of overall CR or better rate, overall MRD- negativity rate, and sustained MRD- negativity demonstrated a treatment effect of D-VRd in the ≥65 years subgroup:

- A higher proportion of participants in the D-VRd arm achieved CR or better compared with the VRd arm (D-VRd 81.9%; VRd 71.3%; odd ratio 1.83).
- A higher proportion of participants achieved MRD-negativity in the D-VRd arm compared with the VRd arm (D-VRd: 67.0%; VRd: 49.4%; odds ratio 2.08).
- A higher proportion of participants achieved sustained MRD-negativity (≥12 months) in the D-VRd arm compared with the VRd arm (D-VRd: 53.2%; VRd: 31.0%; odds ratio 2.53)

Progression-free Survival per Investigator Assessment and Agreement with Computerized Algorithm Analyses

Table 15. Summary of Progression-free Survival Based on Investigator Assessment; Intent-to-treat Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd
Analysis set: intent-to-treat	354	355
Progression-free survival (PFS)		
Number of events (%)	105 (29.7%)	51 (14.4%)
Number of censored (%)	249 (70.3%)	304 (85.6%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	35.94 (30.59, 43.17)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.42 (0.30, 0.59)
6-month PFS rate % (95% CI)	94.5 (91.5, 96.4)	97.1 (94.7, 98.4)
12-month PFS rate % (95% CI)	91.2 (87.6, 93.8)	95.1 (92.2, 96.9)
24-month PFS rate % (95% CI)	85.1 (80.8, 88.5)	93.0 (89.8, 95.3)
36-month PFS rate % (95% CI)	74.8 (69.8, 79.2)	89.4 (85.7, 92.3)
48-month PFS rate % (95% CI)	67.2 (61.7, 72.1)	84.0 (79.1, 87.8)
60-month PFS rate % (95% CI)	NE (NE, NE)	NE (NE, NE)

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; CI = confidence interval; NE = not evaluable.

a - p-value is based on the log-rank test stratified with ISS staging (I, II, vs. III), and cytogenetic risk (high risk vs. standard risk or unknown).

b - Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, vs. III), and cytogenetic risk (high risk vs. standard risk or unknown). A hazard ratio <1 indicates an advantage for D-VRd.

Table 16. Agreement on Disease Progression Assessment Between Algorithm and Investigator; Intent-to-treat Analysis Set (Study 54767414MMY3014)

Investigator Assessment	Computerized Algorithm Assessment			Prevalence Adjusted and Bias Adjusted Kappa (95% CI)	Observed Agreement	Response Rate Difference (95% CI[a]) (Investigator-Algorithm)
	PD	No PD	Total			
PD	122 (96.8%)	4 (3.2%)	126			
No PD	3 (0.5%)	580 (99.5%)	583			
Total	125 (17.6%)	584 (82.4%)	709	0.98 (0.97, 0.99)	99.0%	-0.001 (-0.041, 0.038)

VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; CI = confidence interval; PD = progressive disease.

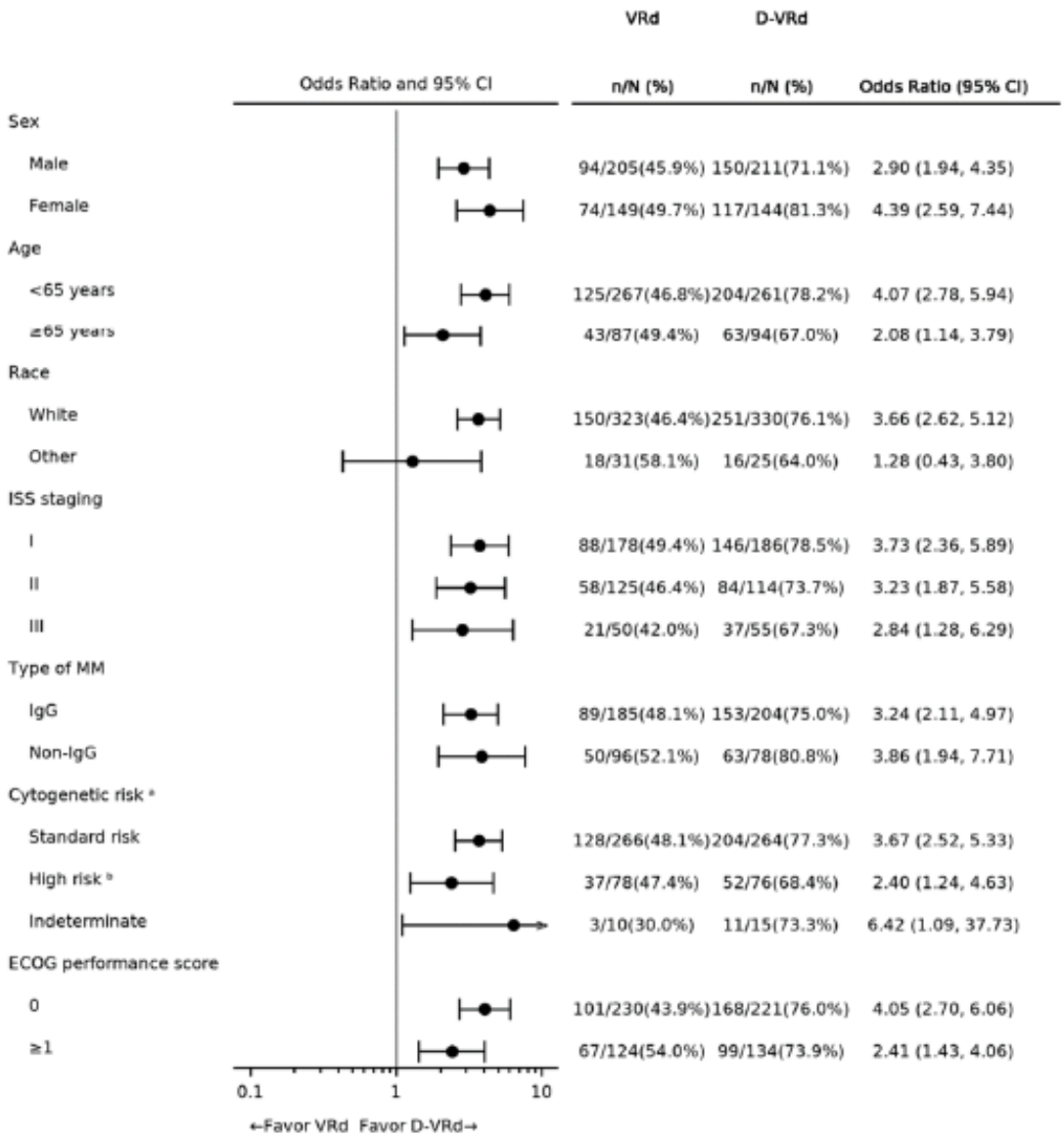
a Wald type confidence interval is provided.

Note: Percentages are calculated based on Total column.

Note: The higher the kappa coefficient, the higher the agreement between algorithm assessment and investigator assessment.

Subgroup Analyses of MRD negativity

Figure 7. Forest Plot of Subgroup Analysis on Overall MRD Negativity Rate by NGS at or below 10^{-5} in Participants with CR or Better; Intent-to-treat Analysis Set (Study 54767414MMY3014)



Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of Efficacy for study MMY3014 (PERSEUS)

Title: A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) vs VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Previously Untreated Multiple Myeloma who are Eligible for High-dose Therapy	
Study identifier	54767414MMY3014 (PERSEUS) EMN17 EudraCT Number: 2018-002992-16 EU Trial Number: 2023-506125-10-00 Clinicaltrials.gov: NCT03710603

Design	Phase 3, randomized, open-label, multicenter study comparing D-VRd versus VRd in participants with newly diagnosed MM who are eligible for ASCT.		
	Study initiation: Screening Phase: Induction / ASCT / Consolidation / Maintenance Phase (Treatment Phase): Follow-up Phase:		03 January 2019 (first participant screened) Starts up to 28 days before randomization Extends from C1D1 to discontinuation of all study treatment Starts when a participant experiences documented disease progression or unacceptable toxicity leading to all study treatment discontinuation or if they have not achieved a response of PR or better by C7D1.
Hypothesis	Superiority of D-VRd over VRd		
Treatments groups	VRd		**Bortezomib** SC injection (1.3 mg/m^2) – D1, D4, D8, D11 during C1 to C6; induction: 4, 28-day cycles (C1 to C4); consolidation: 2, 28-day cycles (C5 to C6). **Lenalidomide** PO (25 mg) - D1 to D21 during C1 to C6; induction: 4, 28-day cycles; consolidation: 2, 28-day cycles. Maintenance: 10 mg daily PO on D1 to D28 (continuously) of each 28-day cycle until PD or unacceptable toxicity. **Dexamethasone** PO (40 mg) on D1 to D4 and D9 to D12 of each 28-day cycle during induction/consolidation (C1 to C6) **ASCT** with high dose melphalan after 4 cycles of induction
	D-VRD		VRd and ASCT as above **Daratumumab** SC (1800 mg) – once every week for C1 to C2, then every 2 weeks for C3 to C6. For maintenance C7+, once every 4 weeks until PD or unacceptable toxicity. Participants with CR or better and sustained MRD-negativity for 12 months will stop daratumumab after a minimum of 24 months of maintenance therapy and restart if loss of CR without PD or loss of MRD-negativity.
Endpoints and definitions	Primary endpoint	PFS by computerised algorithm	Time from the date of randomization to the date of PD (assessed by 2011 IMWG criteria) or death
	Key secondary	Overall CR or better rate	The percentage of ITT participants who achieved CR or sCR status anytime during the study per the 2011 IMWG criteria

	Key secondary	Overall MRD-negativity	The proportion of ITT participants who achieved MRD-negativity (at or below the threshold of 10^{-5}) by bone marrow aspirate and achieve CR or better response at any time after the date of randomization during the study (and prior to PD, subsequent therapy, or both).
	Key secondary	Overall survival	Measured from the date of randomization to the date the participant's death
Database lock	01 August 2023		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, n = 709 Median follow-up of 47.5 months		
Descriptive statistics and estimate variability	Treatment group	D-VRd	VRd
	Number of subjects	355	354
	PFS event by computerised algorithm, n	50	103
	%	14.1%	29.1%
	Overall CR or better rate, n	312	248
	% (95% CI)	87.9% (84.0%, 91.1%)	70.1% (65.0%, 74.8%)
	Overall MRD-negativity	267	168
	% (95% CI)	75.2% (70.4%, 79.6%)	47.5% (42.2%, 52.8%)
	Overall survival, n	34	44
	%	9.6%	12.4%
Effect estimate per comparison	Primary endpoint - PFS by computerised algorithm	Comparison groups	D-VRd vs VRd
		HR[a]	0.42
		95% CI	0.30, 0.59
		P-value[b]	<0.0001
	Secondary endpoint – Overall CR or better	Comparison groups	D-VRd vs VRd
		Odds ratio[c]	3.13
		95% CI	2.11, 4.65
		P-value[d]	<0.0001
	Secondary endpoint – MRD negativity rate (10^{-5})	Comparison groups	D-VRd vs VRd
		Odds ratio[c]	3.40
		95% CI	2.47, 4.69
		P-value[d]	<0.0001
	Secondary endpoint – overall survival	Comparison groups	D-VRd vs VRd
		HR[a]	0.73
		95% CI	0.47, 1.14
		P-value	Not disclosed
Notes	a - Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, vs. III), and cytogenetic risk (high risk vs. standard risk or unknown). b - p-value is based on the log-rank test stratified with ISS staging (I, II, vs. III), and cytogenetic risk (high risk vs. standard risk or unknown). c - Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are ISS staging (I, II, vs. III) and cytogenetic risk (high risk vs. standard risk). d - P-value from the stratified Cochran Mantel-Haenszel Chi-Squared test.		

Clinical studies in special populations

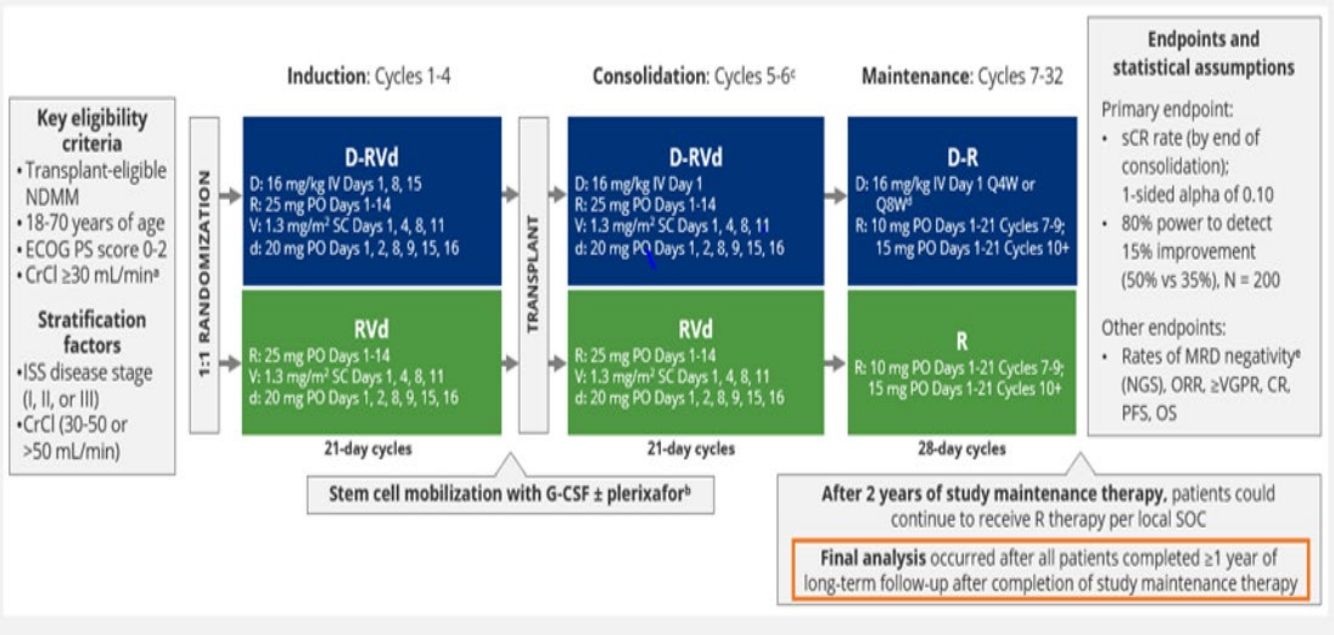
Not applicable.

Supportive study

The GRIFFIN study was a multicentre, randomised, open-label, active-controlled, Phase 2 study, comparing D-VRd versus VRd and recruited in the US only for participants 18 to 70 years of age with NDMM who were eligible for ASCT. The first site was opened on 29 August 2016 and the last participant's last visit occurred on 8 April 2022.

The study design is depicted in **Figure 8**.

Figure 8. GRIFFIN study design



ECOG PS=Eastern Cooperative Oncology Group performance status; CrCl=creatinine clearance; IV=intravenous; PO=oral; SC=subcutaneous; G-CSF=granulocyte colony-stimulating factor; D-R=daratumumab plus lenalidomide; Q4W=every 4 weeks; Q8W=every 8 weeks; NGS=next-generation sequencing; ORR=overall response rate; VGPR=very good partial response; CR=complete response; PFS=progression-free survival; PFS2=PFS on next subsequent line of therapy; OS=overall survival.

The primary endpoint of the study was the proportion of the participants achieving a sCR by the end of post-ASCT consolidation treatment as determined by the validated computer algorithm using the 2016 IMWG criteria. Secondary endpoints included the proportion of participants who achieve PR or better, VGPR or better, CR (or sCR), per IMWG criteria, or MRD-negative status following induction treatment (prior to ASCT), ASCT (prior to start of consolidation treatment), post-ASCT consolidation (after Cycle 6), and maintenance treatment respectively.

The prespecified primary analysis occurred after all randomized patients completed the post-ASCT consolidation disease evaluation or discontinued from study treatment before this time point. A second protocol-specified analysis will be performed after all randomized patients complete the maintenance phase or discontinue from study treatment before completing maintenance.

The primary hypothesis was that patients in the D-VRd group would have an improved rate of sCR by the end of post-ASCT consolidation compared with the VRd group (primary end point), tested at a 1-

sided a of 0.10. All secondary analyses were evaluated using a 2-sided P value (a 0.05) and were not adjusted for multiplicity.

Two hundred twenty-three participants were enrolled/randomized in the GRIFFIN study (16 participants in the safety run-in, 104 participants randomized to the D-VRd group, and 103 participants to the VRd group;).

Among the 207 randomized participants, 201 participants received treatment (D-VRd: 100 [96.2%] participants; VRd: 101 [98.1%] participants;). The median duration of follow-up was 49.6 months for 2 treatment groups combined (D-VRd: 49.8; VRd:49.4 months).

The majority of participants were male (57.0%) and white (78.2%). A total of 15.5% of the participants were black or African American. The median age was 60 years (range: 29 to 70 years) and the median weight was 82.0 kg (range: 37.4 to 158.6 kg). Approximately, half of the participants (103 [50.7%]) had an ECOG score of 1 at baseline.

Both randomization stratification factors, ISS stage and baseline CrCl, were balanced between treatment groups (ISS stage II to III: D-VRd: 54 [51.9%] participants versus VRd: 53 [51.5%] participants, and CrCl 30 to 50 mL/min: 9 [8.7%] participants in each treatment group).

In both the D-VRd and VRd treatment groups, the majority of participants had IgG multiple myeloma (D-VRd: 58.0%; VRd: 55.0%) and measurable disease by serum only (D-VRd: 51.0% participants; VRd: 58.3% participants). Approximately half of the participants (D-VRd: 47.1% participants; VRd: 48.5% participants) had ISS Stage I disease. High-risk cytogenetic abnormality, defined as any of the following: del(17p), t(4;14), and t(14;16), was balanced in both arms, (D-VRd: 16.3%; VRd: 14.4%).

The median duration of study treatment was 32.5 months in the D-VRd group and 27.5 months in the VRd group.

The median number of treatment cycles received was 32 cycles in the D-VRd arm and 24.5 cycles in the VRd arm. After completion of the per protocol maintenance (24 months), additional lenalidomide maintenance was received by 63 (63.6%) participants in the D-VRd group for a median of 16.9 months while 42 (41.2%) of participants in the VRd group received this additional maintenance therapy for a median of 14.8 months.

Primary Efficacy Endpoint – sCR by the end post-ASCT consolidation

At the time of primary analysis (CCO 25 January 2019) in 196 response-evaluable participants (D-VRd: 99 participants and VRd: 97 participants), the sCR rate by the end of post-ASCT consolidation phase was higher in the D-VRd group (42.4%) compared with the VRd group (32.0%; odds ratio [D-VRd versus VRd] was 1.57 with 95% CI: 0.87, 2.82; 2-sided p-value=0.1359 equivalent to 1-sided p-value=0.068) which was statistically significant at the pre-set 1-sided alpha level of 0.1.

Progression-free Survival

At the time of the final analysis with a median follow-up of 49.6 months, 11 (10.6%) and 18 (17.5%) PFS events as assessed by the computerized algorithm occurred in the D-VRd and VRd groups, respectively. The HR (D-VRd versus VRd) was 0.45 (95% CI: 0.21, 0.95; 2-sided nominal p-value=0.0324) and the median PFS was not reached in either treatment group. The estimated 48-month PFS rate was 87.2% in the D-VRd group and 70.0% in the VRd group. The majority of participants in the D-VRd and VRd groups (89.4% and 82.5% of participants) were censored for PFS, with leading reasons of study cutoff (D-VRd: 68.8%; VRd: 48.2%) and subsequent antimyeloma therapy use (D-VRd: 16.1%; VRd: 30.6%).

Pre-specified subgroup analyses of PFS, including that of participants with high-risk cytogenetic abnormalities, demonstrated that the HR point estimates for the treatment effect of D-VRd over VRd were generally in favour of D-VRd and consistent with the whole ITT population except participants with non-IgG myeloma.

Of note, in the age ≥65y the HR was 0.29 (0.06, 1.48) compared with the HR of 0.45 (0.21, 0.95) in the ITT population.

CR or Better Rate

By the end of the maintenance phase, the rate of CR or better (sCR + CR) was higher for the D-VRd group (79.8%) than the VRd group (57.3%) as assessed by ITT analysis set (nominal 2-sided p=0.0007).

Minimal Residual Disease

The proportion of participants with both MRD-negativity (10^{-5}) and a response of CR or better by the end of maintenance phase was higher in the D-VRd group (61.5%) than in the VRd group (27.2%) (odds ratio=4.20; 95% CI: 2.34, 7.56; nominal 2-sided p-value<0.0001).

The rate of MRD-negativity (10^{-5}) and a response of CR or better by the end of consolidation was higher in the D-VRd group (32.7%) vs VRd group (10.7%).

The sustained (≥1-year) MRD-negativity rate (10^{-5}) was higher in participants in the D-VRd group (44.2%) compared with the participants in the VRd group (13.6%) (odds ratio: 5.00; 95% CI: 2.50, 9.99; nominal 2-sided p<0.0001).

Overall Survival

With a median follow-up of 49.6 months, OS data were immature. A total of 14 deaths (D-VRd: 7 [6.7%], VRd: 7 [6.8%]) were reported in the randomized treatment groups. The median OS was not reached in either treatment group. The HR (D-VRd versus VRd) was 0.90 (95% CI: 0.31, 2.56; nominal 2-sided p-value=0.8408).

Overall Response Rate

By the end of induction:

- ORR (sCR + CR + VGPR + PR) was higher in the D-VRd group compared with the VRd group (93.3% versus 86.4%) (odds ratio [D-VRd versus VRd] 2.22 with 95% CI: 0.85, 5.78; nominal 2-sided p-value=0.0996) in ITT analysis set.
- VGPR or better rate (D-VRd 68.3%, VRd 53.4%, OR 1.83, 95% CI: 1.04, 3.21; nominal 2-sided p-value=0.0332).
- CR or better rate (sCR + CR) was higher for the D-VRd group (18.3%) than the VRd group (12.6%) as assessed by ITT analysis set (nominal 2-sided p=0.2903).
- sCR rate (D-VRd 11.5%, VRd 6.8%, OR 1.77, 95% CI: 0.66, 4.72; nominal 2-sided p-value=0.2538).

Post-ASCT:

- ORR (sCR + CR + VGPR + PR), was higher in the D-VRd group compared with the VRd group (94.2% versus 86.4%) (odds ratio [D-VRd versus VRd] 2.63 with 95% CI: 0.96, 7.20; nominal 2-sided p-value=0. 0549) in ITT analysis set.
- VGPR or better rate (D-VRd 82.7%, VRd 62.1%, OR 2.85, 95% CI:1.49, 5.44; nominal 2-sided p-value=0.0010).
- CR or better rate (sCR + CR) was higher for the D-VRd group (26.0%) than the VRd group (18.4%) as assessed by ITT analysis set (nominal 2-sided p=0.2048).
- sCR rate (D-VRd 20.2%, VRd 13.6%, OR 1.62, 95%CI:0.76,3.43; nominal 2-sided p-value=0.2139).

End Consolidation:

- ORR (sCR + CR + VGPR + PR), was higher in the D-VRd group compared with the VRd group (94.2% versus 86.4%) (odds ratio [D-VRd versus VRd] 2.63 with 95% CI: 0.96, 7.20; nominal 2-sided p-value=0. 0549) in ITT analysis set.
- VGPR or better rate was higher in the D-VRd group compared with the VRd group (D-VRd: 86.5%, VRd: 68.9%), (odds ratio [D-VRd versus VRd] 2.84 with 95% CI: 1.41, 5.74; nominal 2-sided p-value=0. 0025).
- CR or better (sCR + CR) was higher for the D-VRd group (49.0%) than the VRd group (39.8%) as assessed by ITT analysis set (nominal 2-sided p=0.1874).
- sCR, see section on primary endpoint.

By the end of maintenance:

- ORR (sCR + CR + VGPR + PR) was higher in the D-VRd group compared with the VRd group (95.2% versus 87.4%) (odds ratio [D-VRd versus VRd] 2.93 with 95% CI: 0.99, 8.64; nominal 2-sided p-value=0.0448) in ITT analysis set.
- VGPR or better rate was 92.3% in the D-VRd group and 73.8% in the VRd group (odds ratio [D-VRd versus VRd] 4.06 with 95% CI: 1.75, 9.43; nominal 2-sided p-value=0.0004).
- sCR rate was 64.4% and 45.6% (odds ratio [D-VRd versus VRd] 2.12 with 95% CI: 1.22, 3.71; nominal 2-sided p-value=0.0080) in the D-VRd and VRd treatment groups, respectively.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study MMY3014

Study MMY3014 was a phase 3, randomised, open-label, multicentre study comparing D-VRd versus VRd in participants with newly diagnosed MM who were eligible for ASCT. Participants were randomised in a 1:1 ratio, stratified by ISS Stage I, II, or III disease (β-2 microglobulin and albumin) and cytogenetics (standard-risk or high-risk, which is defined by the presence of del17p, t[4;14] or t[14;16]). The treatment phase included four elements: Induction treatment, ASCT, consolidation treatment and maintenance treatment (D-R vs. R).

The stratification factors have prognostic and predictive impact in this setting and are deemed appropriate. Treatment regiments were standard and are acceptable.

The study design does not allow for evaluation of the treatment effect of adding daratumumab to VRd in the induction phase or consolidation phase or to lenalidomide in the maintenance phase respectively, as the study did not include a randomisation pre-consolidation or a randomisation pre-maintenance. Rather, the treatment effect of adding daratumumab to the VRd backbone and to lenalidomide maintenance has to be considered across all three treatment phases as a whole. Hence the proposed wording of the new indication by the MAH, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant, is supported without specifying treatment phases (induction, consolidation and maintenance).

Inclusion and exclusion criteria employed in the study adequately reflects patients for whom high-dose chemotherapy and autologous stem cell transplantation would be part of the intended treatment plan. However, it should be noted that a screening period of 28 days before randomization to treatment excluded patients with NDMM who need acute or sub-acute anti-myeloma treatment with more than just

40mg x 4 of dexamethasone to alleviate severe kidney disease, severe hypercalcemia or significant bone disease.

The exclusion of NDMM patients with an acute or sub-acute presentation at diagnosis can be considered justifiable as management of acutely ill NDMM patients in the strict framework of a clinical trial can be complicated. However, this should be kept in mind when extrapolating trial results to non-trial settings.

The primary endpoint in the study was PFS by computerised algorithm defined as time from the date of randomisation to the date of PD (assessed by 2011 IMWG criteria) or death. The key secondary endpoints were overall CR or better rate anytime during the study, overall MRD-negativity rate achieved at any time during the study, and OS. The choice of endpoints and objectives in this clinical setting is considered appropriate.
The use of the 2011 IMWG consensus recommendations for multiple myeloma treatment response criteria is also supported.

Sample size calculations appear appropriate and considered relevant factors such as enrolment period and expected HR for PFS. The primary endpoint and key secondary endpoints were evaluated in the ITT population. The first interim analysis was to be performed at approximately 143 PFS events, representing 50% of the total planned events. If the superiority of D-VRd over VRd was established in either of two planned interim analyses, it would serve as the primary PFS analysis. Assuming that 143 and 185 PFS events, respectively, are observed at the first and second PFS interim analyses, the two-sided alpha to be spent in the two interim analyses would be 0.0112 and 0.0126. Hierarchical testing was used to control the overall family-wise Type I error rate at 5% two-sided across primary and key secondary hypotheses, with specific alpha-spending functions for group sequential testing. The Hwang-Shih-DeCani alpha-spending function with a gamma parameter of -2.5 determined the significance levels at interim analyses. Secondary endpoints were tested sequentially only if PFS was significant. Hierarchical testing ensured strong control of the overall family-wise Type I error rate at 0.05. This approach to prevent Type I error inflation was endorsed.

709 patients were randomly assigned 1:1 to D-VRd (355 patients) or VRd (354 patients). As of the data cutoff date (01 August 2023), the median duration of follow up was 47.5 months. Of the 709 randomized participants, 351 participants in the D-VRd arm and 347 participants in the VRd arm received study treatment. Fewer participants in the D-VRd arm (91 [25.9%]) discontinued treatment compared with the VRd arm (188 [54.2%]). The majority of discontinuations occurred during induction and maintenance. The most common reasons for discontinuation of all components of study treatment (>10% of total in either arm) were adverse events (D-VRd: 9.1%; VRd: 22.5%) and progressive disease (D-VRd: 8.3%; VRd: 20.7%). The overall higher rate of discontinuation in the VRd arm was primarily driven by study design. The participants in the VRd arm only received treatment with lenalidomide during maintenance therapy, thus any discontinuation of lenalidomide led to discontinuation of all study drugs. In contrast, in the D-VRd arm, if participants discontinued lenalidomide during maintenance therapy, daratumumab study treatment was not discontinued.

Major protocol amendments were appropriately justified. Modifications of inclusion and exclusion criteria were of clarifying nature and are not believed to have altered the patient population that was intended for enrolment into the trial.

GRIFFIN study

Overall study design was similar between MMY3014 and GRIFFIN. However, VRd and D-VRd cycle length varied between the studies with 4-week cycles and 3-week cycles respectively. There were also differences in the dosing regimens of all administered medicines.

The primary endpoint was sCR at the end of post-ASCT consolidation. sCR response was not evaluated on the ITT set but the on the response evaluable set.

The differences in medication dosing and strength are overall considered minor and do not preclude that the GRIFFIN study can be considered as supportive to study MMY3014 with regard to efficacy claims.

Efficacy data and additional analyses

Study MMY3014

The demographic and clinical characteristics of the patients at baseline were generally balanced in the two groups and reflect a rather fit patient population with NDMM with low levels of comorbidity that could go up to 28 days without initiation of anti-myeloma treatment other than 4 x 40mg of dexamethasone and thus selecting a population with less aggressive debut of multiple myeloma without immediate need of treatment. The median age was 60.0 (range 31-70) years. The majority of the participants were white (92.1%) and had an ECOG performance score of 0 (63.6%) or 1 (31.3%).

The number of participants with SLiM-CRAB criteria (i.e., presence of biomarkers of malignancy) at diagnosis was low in both treatment arms (D-VRd: 52 [14.7%]; VRd: 65 [18.5%]) but with a slight imbalance favouring the VRd arm. Stratification factors of cytogenetics and ISS stage were balanced between the two treatment arms. Median time in months from MM diagnosis to randomisation was 1.12 months in the VRd arm and 1.18 months in the D-VRD arm.

At the CCO on 01 August 2023, when the first planned interim analysis was conducted, a total of 153 PFS events (D-VRd: 50/355 (14.1%); VRd: 103/354 (29.1%)) had been observed, with a median follow-up of 47.51 months (D-VRd: 47.57 months; VRd: 47.38 months).

The addition of daratumumab to VRd resulted in a statistically significant improvement in the primary endpoint PFS with a HR=0.42 (95% CI: 0.30, 0.59; 2-sided p <0.0001) compared to VRd alone. The p-value crossed the prespecified stopping boundary of 0.0126 in favour of the D-VRd arm, turning the first interim analysis for PFS into the primary analysis. The median PFS had not been reached in either treatment arm (48-month PFS rate: D-VRd: 84.3%; VRd: 67.7%). The PFS benefit was generally consistent across prespecified subgroups (ISS stage, cytogenetic risk, and baseline ECOG performance score), showing improvement for participants in the D-VRd arm compared with participants in the VRd arm, with the exception of the ≥65 years subgroup (HR=0.97 [95% CI: 0.52, 1.81]). In this subgroup, there was an imbalance in the cytogenetic high-risk category (D-VRd 25.5% vs VRD 19.5%), which may have contributed to the observed HR in this particular age subgroup. Overall, there is no basis for a restriction of the indication based on age. The final analysis for PFS (285 events) is projected to occur in 2028-2029 and the CHMP recommended that these results should be submitted when available.

The addition of daratumumab to VRd resulted in a statistically significant improvement in the key secondary endpoint overall CR or better rate compared with VRd alone with an absolute increase of 17.8% favouring treatment with D-VRd (D-VRd: 87.9%; VRd: 70.1%; odds ratio=3.13 with 95% CI: 2.11, 4.65; 2-sided p <0.0001).

A higher proportion of patients achieved the key secondary endpoint of MRD-negativity at the 10^{-5} threshold in the D-VRd arm compared with the VRd arm (D-VRd: 75.2%; VRd: 47.5%; odds ratio=3.4; 95% CI: 2.47, 4.69; 2-sided p <0.0001), with an absolute difference of 27.7% favouring treatment with D-VRd.

With an overall median follow-up of 47.51 months the OS data are still immature. With a total of 78 deaths (D-VRd: 34; VRd: 44), the median OS was not reached for either treatment arm. The analysis reveals no suspected detriment in the D-VRd arm with an estimated HR of 0.73 ((95% CI: 0.47, 1.14).

The remaining endpoints were not type 1 error controlled, but favoured D-VRd treatment over VRd treatment with regard to MRD-negativity at 10^{-6} threshold, MRD-negativity (10^{-5}) post-consolidation, sustained MRD-negativity (>12 months MRD negativity at the 10^{-5} threshold, and time to subsequent anti-myeloma treatment.

Treatment with either D-VRd or VRd led to comparable improvements in the measured PROs including increased physical function score, reduced fatigue symptom score and reduced pain symptom score.

Regarding ASCT, a higher number of patients failed stem cell mobilization in the D-VRd arm (9 vs 3) suggesting that the addition of daratumumab to VRd induction can reduce the probability for a successful stem cell harvest. Despite increased use of plerixafor for stem cell mobilization and lower amount of collected $CD34^+$ stem cells in the D-VRd arm, similar rates of hematopoietic reconstitution were observed among transplanted participants for both treatment arms (D-VRd: 99.7% (314/315); VRd: 99.3% (300/302)). Median time to engraftment post-ASCT was 14.0 days for each treatment arm.

Despite the higher number of patients failing stem cell mobilization in the D-VRd arm, it should be noted that the frequency of patients who made it to successful engraftment post ASCT based on the ITT population was higher in the D-VRd arm compared to the VRd arm with 88.5% (314/355) vs 84.7% (300/354) respectively.

GRIFFIN study

The sCR rate by the end of post-ASCT consolidation phase was higher in the D-VRd group (42.4%) compared with the VRd group (32.0%; odds ratio [D-VRd versus VRd] was 1.57 with 95% CI: 0.87, 2.82). A post-hoc analysis of sCR rate per ITT analysis was similar with the analysis performed by the response-evaluable analysis set: sCR of 40.4% in the D-VRd group and 30.1% in the VRd group (odds ratio [D-VRd versus VRd] was 1.58, 95% CI: 0.88, 2.82).

Pre-specified subgroup analyses of PFS, including that of participants with high-risk cytogenetic abnormalities, demonstrated that the HR point estimates for the treatment effect of D-VRd over VRd were generally in favour of D-VRd and consistent with the whole ITT population except participants with non-IgG myeloma.

Of note, in the age group (≥65y), the HR for PFS was 0.29 (0.06, 1.48) compared with the HR of 0.45 (0.21, 0.95) in the ITT population. So, the reduced efficacy seen in MMY3014 study in that subgroup with regard to PFS was not observed here.

Other endpoints in the study also seem to favour D-VRd compared to VRd.

In conclusion, the GRIFFIN study is considered supportive of the efficacy results observed in the main study MMY3014 and no major conflicting findings between the studies were observed.

2.4.3. Conclusions on the clinical efficacy

Results from the interim analysis of study MMY3014 showed a statistically significant relevant improvement in PFS from the addition of daratumumab to VRd in patients with newly diagnosed multiple myeloma. This improvement is considered clinically significant and is supported by secondary endpoints such as statistically significant improvement in overall CR or better treatment response rates and statistically significant higher proportion of patients achieving MRD negativity at the 10^{-5} threshold. OS data are immature but do not show any sign of detriment in the experimental arm.

Supportive evidence of efficacy in support of D-VRd in the claimed indication comes from the GRIFFIN study.

2.5. Clinical safety

Introduction

The most frequent adverse reactions of any grade (≥ 20% patients) observed in clinical trials with daratumumab (either intravenous or subcutaneous formulations) administered either as monotherapy or combination treatment were Infusion related reactions (IRRs), fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea, atrial fibrillation and syncope.

The safety profile of the daratumumab subcutaneous formulation was similar to that of intravenous formulation with the exception of a lower rate of IRRs. In the phase III study MMY3012, neutropenia was the only adverse reaction reported at ≥ 5% higher frequency for daratumumab subcutaneous formulation compared to intravenous daratumumab (grade 3 or 4: 13% vs 8%, respectively).

Patient exposure

The pivotal safety data in support of this application comments from the Phase 3 Study MMY3014 and a summary of the duration of treatment in that trial is presented in **Table 18**.

Table 18. Summary of Duration of Treatment, by Treatment Phase; Safety Analysis Set (Study 54767414MMY3014)

	VRd	D-VRd
Analysis set: safety	347	351
Treatment duration (months)		
N	347	351
Mean (SD)	34.055 (16.3802)	39.993 (13.4519)
Median	42.185	45.733
Range	(0.07; 53.91)	(0.49; 54.34)
Induction treatment[a]		
N	347	351
Mean (SD)	3.914 (1.4112)	3.957 (1.3419)
Median	3.450	3.450
Range	(0.07; 11.37)	(0.49; 10.32)
Pre-ASCT[b]		
N	303	315
Mean (SD)	1.952 (0.9538)	2.105 (1.1110)
Median	1.774	1.873
Range	(0.10; 7.36)	(0.10; 7.85)
ASCT[c]		
N	294	309
Mean (SD)	2.588 (0.7559)	2.562 (0.9796)
Median	2.595	2.497
Range	(0.92; 6.37)	(0.72; 11.96)
Consolidation treatment[d]		
N	262	274
Mean (SD)	1.626 (0.1776)	1.633 (0.2418)
Median	1.610	1.610
Range	(0.53; 2.53)	(0.46; 2.40)
Induction/Pre-ASCT/ASCT/Consolidation[e]		
N	292	303
Mean (SD)	9.984 (1.5056)	9.976 (1.4511)
Median	9.692	9.659
Range	(7.13; 17.35)	(6.28; 16.13)
Maintenance treatment[f]		
N	300	322
Mean (SD)	28.448 (12.1868)	32.871 (8.7450)

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.

a - Duration of induction treatment: For subjects who received induction treatment, from first induction dose date to the last induction dose date. For subject with mobilization occurred within the induction phase, the duration of mobilization was not counted in.

b - Duration of Pre-ASCT: For subjects receive mobilization therapy, from the day after the last dose of induction, to the day before the start date of melphalan administration. Subjects who were not proceed to transplant were not taken into account for this calculation.

c - Duration of ASCT: For subjects who proceed to transplant, from the start date of melphalan administration, to the day before the first dose date of consolidation phase, or the day before the first date of maintenance phase treatment which was after the ASCT for subjects without the consolidation phase, whichever is earlier. Subjects who were end of treatment during ASCT phase were not taken into account for this calculation.

d - Duration of consolidation treatment: from first consolidation dose date to the last consolidation dose date.

e - Duration of induction/Pre-ASCT/ASCT/consolidation treatment: (a) For subjects received consolidation after having received ASCT, from first induction dose date to the last consolidation dose date. (b) For subjects received ASCT after 6 cycles of induction, from first induction dose date to the day before maintenance treatment start date, or the date of end-of treatment visit, whichever is earlier. Subjects who received both ASCT and consolidation, or received ASCT after 6 cycles of induction were taken into account for this calculation.

f - Duration of maintenance treatment: from first maintenance dose date to the last maintenance dose date.

Note: Induction phase includes patients who had more than 4 cycles treatment induction phase due to COVID-19 pandemic or patients who did not get transplant for other reasons.

In Study MMY3014, dose modifications consisted of cycle delays, dose delays, skipped doses, or dose reductions. Dose modifications were reported in participants, as follows:

- **Cycle delays**: Cycle delays were reported in a higher proportion of participants in the D-VRd arm compared with the VRd arm (D-VRd: 89.5%; VRd: 80.7%). The most common reason for cycle delays was AEs (D-VRd: 74.1%; VRd: 63.1%) and "other" reasons (D-VRd: 68.7%; VRd: 51.3%). Overall, the majority of cycle delays occurred during maintenance (D-VRd: 91.6%; VRd: 80.0%), consistent with the longer duration of maintenance treatment at the time of CCO.
- **Dose delays**:
    - Daratumumab, D-VRd, 7.1%, with 4.6% during induction
    - Bortezomib, D-VRd: 0; VRd: 1.7%
    - Dexamethasone, D-VRd: 1.4%; VRd: 1.7%
- **Skipped doses:**
    - Daratumumab, D-VRd, 45.3%, with 33.3% of participants skipping an injection during induction
    - Bortezomib, D-VRd: 43.3%; VRd: 43.8%, primarily for AEs (D-VRd: 37.6%; VRd: 35.2%)
    - Lenalidomide, D-VRd: 84.3%; VRd: 76.7%, predominantly occurring during maintenance (D-VRd: 81.4%; VRd: 72.3%), and primarily for AEs (D-VRd: 74.4%; VRd: 62.8%)
    - Dexamethasone, D-VRd: 28.8%; VRd: 25.1%
- **Dose interruptions**: A low proportion of participants had daratumumab injection interruption (2.0%), and no participants aborted the injection.
- **Dose reductions**:
    - Bortezomib, D-VRd: 27.6%; VRd: 26.2%, primarily for AEs (D-VRd: 27.4%; VRd: 25.9%)
    - Lenalidomide, D-VRd: 63.8%; VRd: 51.3%, predominantly occurring during maintenance (D-VRd: 55.9%; VRd: 49.3%), and primarily for AEs (D-VRd: 61.3%; VRd: 49.9%)

- Dexamethasone, D-VRd; 33.9%; VRd: 29.4%

- **Treatment discontinuations:**
  - Daratumumab, 2.6%, with AEs as the most common reason (2.3%)
  - Bortezomib, D-VRd: 10.0%; VRd: 8.1%, primarily for AEs (D-VRd: 9.7%; VRd: 7.5%)
  - Lenalidomide, D-VRd: 26.5%; VRd: 19.6%, primarily for AEs (D-VRd: 22.5%; VRd: 12.4%)
  - Dexamethasone, D-VRd: 2.6%; VRd: 3.2%

Supportive safety information is provided by the GRIFFIN study (described in Section 2.4 of this report) and the PLEAIDES study, a multicentre, open-label, Phase 2 study to investigate the efficacy and safety of daratumumab SC in combination with 4 standard multiple myeloma treatment regimens: VRd in participants with NDMM who were transplant eligible; VMP in participants with NDMM who were ineligible for transplant; and Rd and Kd in participants with relapsed or refractory multiple myeloma. Participants in the D-VRd cohort (67 patients) received D-VRd treatment in 21-day cycles for a maximum of 4 cycles. Treatment consisted of daratumumab SC 1800 mg weekly for Cycles 1 to 3 and on Day 1 of Cycle 4; bortezomib SC 1.3 mg/m2 on Days 1, 4, 8 and 11 of each cycle; lenalidomide PO at 25 mg on Days 1 to 14 of each cycle; and dexamethasone PO or IV 20 mg on Days 1, 2, 8, 9, 15 and 16 of each cycle.

In the GRIFFIN study, in the D-VRd and VRd groups, the median duration of study treatment was 32.5 and 27.5 months, respectively, as per study design with fixed duration of maintenance for 24 months only then SOC lenalidomide maintenance per investigator discretion. The median number of treatment cycles received was 32 cycles in the D-VRd arm and 24.5 cycles in the VRd arm. After completion of the per protocol maintenance (24 months), additional lenalidomide maintenance was received by 63 participants (63.6%) in the D-VRd group for a median of 16.9 months while 42 participants (41.2%) in the VRd group received this additional maintenance therapy for a median of 14.8 months.

In the PLEIADES study, participants in the D-VRd cohort received a median of 4 cycles of treatment as per study design for induction only, over a median duration of 2.6 months.

Adverse events

An overview of the treatment emergent adverse events (TEAEs) reported Study MMY3014 is summarised in **Table 19**.

Table 19. Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study MMY3014)

	VRd	D-VRd
Analysis set: safety	347	351
Any TEAE	344 (99.1%)	349 (99.4%)
At least one related[a]	332 (95.7%)	347 (98.9%)
Maximum toxicity grade		
Grade 1	4 (1.2%)	2 (0.6%)
Grade 2	42 (12.1%)	24 (6.8%)
Grade 3	199 (57.3%)	193 (55.0%)
Grade 4	83 (23.9%)	117 (33.3%)
Grade 5	16 (4.6%)	13 (3.7%)
Any serious TEAE	171 (49.3%)	200 (57.0%)
At least one related[a]	65 (18.7%)	103 (29.3%)
TEAE leading to discontinuation of study treatment[b]	74 (21.3%)	31 (8.8%)
COVID-19	1 (0.3%)	1 (0.3%)

	VRd	D-VRd
TEAE leading to discontinuation of daratumumab[c]	0	34 (9.7%)
At least one related to daratumumab	0	13 (3.7%)
TEAE leading to discontinuation of bortezomib[c]	41 (11.8%)	43 (12.3%)
At least one related to bortezomib	27 (7.8%)	36 (10.3%)
TEAE leading to discontinuation of lenalidomide[c]	81 (23.3%)	95 (27.1%)
At least one related to lenalidomide	52 (15.0%)	64 (18.2%)
TEAE leading to discontinuation of dexamethasone[c]	22 (6.3%)	17 (4.8%)
At least one related to dexamethasone	9 (2.6%)	10 (2.8%)
TEAE with outcome of death	16 (4.6%)	13 (3.7%)
At least one related[a]	4 (1.2%)	3 (0.9%)
Death due to COVID-19	1 (0.3%)	4 (1.1%)
TEAE of COVID-19	87 (25.1%)	133 (37.9%)
Serious TEAE of COVID-19	10 (2.9%)	23 (6.6%)

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.
Key: TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 4 study treatments: daratumumab, bortezomib, lenalidomide and dexamethasone.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
[c] Includes those subjects indicated as having discontinued specific study treatment due to an adverse event on the adverse event CRF page.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Percentages are calculated with the number of subjects in each group as denominator.

All participants in the D-VRd and VRd treatment groups experienced at least one TEAE in the GRIFFIN study. A total of 46.5% and 52.0% of participants in the D-VRd and VRd treatment groups, respectively, experienced at least one SAE. TEAEs leading to study treatment discontinuation were reported in 29.3% of participants in the D-VRd treatment group and 29.4% of participants in the VRd treatment group. Death due to a TEAE was reported in 1 (1.0%) participant each in the D VRd and VRd treatment groups.

TEAEs were overall evenly distributed in the GRIFFIN study except grade 3 and 4 events that occurred with a slightly higher rate in the D-VRd arm compared with the VRd arm (84.8% vs. 79.4%).

In the PLEIADES study, all participants in the D-VRd cohort were reported as having a TEAE. Grade 3 or 4 TEAEs occurred in 58.2% of participants in the D-VRd cohort. Treatment-emergent SAEs were reported in 28.4% of participants in the D VRd cohort and 1 (1.5%) participant had a Grade 5 TEAE leading to death. TEAEs leading to study treatment discontinuation were reported in 1 (1.5%) participant in the D VRd cohort.

Grade 3 and 4 TEAEs and treatment-emergent SAEs was less common in the PLEAIDES trial compared with study MMY3014 and the GRIFFIN study. This is believed to be due to the fact that the PLEIADES study only covered induction treatment.

The most commonly reported TEAEs (≥10% in either treatment arm) and Grade 3 or 4 TEAEs ((≥5% in either treatment arm are presented in **Table** 20 and **Table** 21 respectively.

Table 20. Treatment-emergent Adverse Events by System Organ Class and Preferred Term (at Least 10% in Either VRd or D-VRd); Safety Analysis Set (Study MMY3014)

	VRd	D-VRd
Analysis set: safety	347	351
Total number of subjects with TEAE	344 (99.1%)	349 (99.4%)
MedDRA System Organ Class / Preferred Term		
Infections and infestations	266 (76.7%)	305 (86.9%)
COVID-19	83 (23.9%)	123 (35.0%)
Upper respiratory tract infection	87 (25.1%)	111 (31.6%)
Bronchitis	39 (11.2%)	68 (19.4%)
Pneumonia	38 (11.0%)	64 (18.2%)
Nasopharyngitis	39 (11.2%)	58 (16.5%)
Blood and lymphatic system disorders	254 (73.2%)	292 (83.2%)
Neutropenia	204 (58.8%)	243 (69.2%)
Thrombocytopenia	119 (34.3%)	170 (48.4%)
Anaemia	72 (20.7%)	78 (22.2%)
Febrile neutropenia	38 (11.0%)	34 (9.7%)
Gastrointestinal disorders	268 (77.2%)	287 (81.8%)
Diarrhoea	188 (54.2%)	214 (61.0%)
Constipation	118 (34.0%)	119 (33.9%)
Nausea	58 (16.7%)	71 (20.2%)
Vomiting	28 (8.1%)	38 (10.8%)
Abdominal pain	37 (10.7%)	31 (8.8%)
General disorders and administration site conditions	255 (73.5%)	265 (75.5%)
Pyrexia	109 (31.4%)	111 (31.6%)
Asthenia	89 (25.6%)	94 (26.8%)
Fatigue	92 (26.5%)	84 (23.9%)
Oedema peripheral	74 (21.3%)	72 (20.5%)
Influenza like illness	33 (9.5%)	39 (11.1%)
Nervous system disorders	253 (72.9%)	262 (74.6%)
Peripheral sensory neuropathy	179 (51.6%)	188 (53.6%)
Paraesthesia	42 (12.1%)	46 (13.1%)
Headache	37 (10.7%)	31 (8.8%)
Musculoskeletal and connective tissue disorders	197 (56.8%)	215 (61.3%)
Back pain	66 (19.0%)	80 (22.8%)
Muscle spasms	56 (16.1%)	67 (19.1%)
Arthralgia	69 (19.9%)	62 (17.7%)
Pain in extremity	38 (11.0%)	40 (11.4%)
Skin and subcutaneous tissue disorders	179 (51.6%)	189 (53.8%)
Rash	94 (27.1%)	82 (23.4%)
Respiratory, thoracic and mediastinal disorders	132 (38.0%)	171 (48.7%)
Cough	51 (14.7%)	85 (24.2%)
Dyspnoea	24 (6.9%)	37 (10.5%)
Metabolism and nutrition disorders	119 (34.3%)	141 (40.2%)
Hypokalaemia	44 (12.7%)	51 (14.5%)
Psychiatric disorders	106 (30.5%)	132 (37.6%)
Insomnia	61 (17.6%)	95 (27.1%)
Investigations	104 (30.0%)	111 (31.6%)
Alanine aminotransferase increased	51 (14.7%)	57 (16.2%)
Vascular disorders	87 (25.1%)	100 (28.5%)
Eye disorders	63 (18.2%)	70 (19.9%)
Injury, poisoning and procedural complications	58 (16.7%)	69 (19.7%)
Cardiac disorders	35 (10.1%)	60 (17.1%)
Renal and urinary disorders	41 (11.8%)	57 (16.2%)

	VRd	D-VRd
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	33 (9.5%)	47 (13.4%)
Hepatobiliary disorders	34 (9.8%)	39 (11.1%)
Ear and labyrinth disorders	29 (8.4%)	37 (10.5%)

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.
Key: TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Percentages are calculated with the number of subjects in each group as denominator.
Note: Adverse events are coded using MedDRA version 26.0.

Table 21. Treatment-emergent Grade 3 or 4 Adverse Events by System Organ Class and Preferred Term (at Least 5% in Either VRd or D-VRd); Safety Analysis Set (Study MMY3014)

	VRd	D-VRd
Analysis set: safety	347	351
Total number of subjects with Grade 3 or 4 TEAE	297 (85.6%)	321 (91.5%)
MedDRA System Organ Class / Preferred Term		
Blood and lymphatic system disorders	213 (61.4%)	261 (74.4%)
Neutropenia	177 (51.0%)	218 (62.1%)
Thrombocytopenia	60 (17.3%)	102 (29.1%)
Febrile neutropenia	35 (10.1%)	33 (9.4%)
Anaemia	22 (6.3%)	21 (6.0%)
Infections and infestations	95 (27.4%)	124 (35.3%)
Pneumonia	21 (6.1%)	37 (10.5%)
Gastrointestinal disorders	68 (19.6%)	82 (23.4%)
Diarrhoea	27 (7.8%)	37 (10.5%)
Stomatitis	20 (5.8%)	21 (6.0%)
Nervous system disorders	35 (10.1%)	46 (13.1%)
General disorders and administration site conditions	41 (11.8%)	41 (11.7%)
Fatigue	18 (5.2%)	10 (2.8%)
Investigations	32 (9.2%)	30 (8.5%)
Alanine aminotransferase increased	18 (5.2%)	18 (5.1%)
Respiratory, thoracic and mediastinal disorders	20 (5.8%)	27 (7.7%)
Metabolism and nutrition disorders	32 (9.2%)	26 (7.4%)
Skin and subcutaneous tissue disorders	27 (7.8%)	25 (7.1%)
Vascular disorders	19 (5.5%)	24 (6.8%)
Cardiac disorders	9 (2.6%)	23 (6.6%)
Hepatobiliary disorders	11 (3.2%)	21 (6.0%)
Psychiatric disorders	19 (5.5%)	21 (6.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (3.7%)	18 (5.1%)
Musculoskeletal and connective tissue disorders	19 (5.5%)	14 (4.0%)

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.
Key: TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Percentages are calculated with the number of subjects in each group as denominator.
Note: Adverse events are coded using MedDRA version 26.0.

In the GRIFFIN study, the most frequently reported TEAEs in either treatment group were fatigue (D-VRd: 71.7%; VRd: 61.8%), upper respiratory tract infection (D-VRd: 67.7%; VRd: 50%), diarrhoea (D VRd: 66.7%; VRd: 54.9%) and neutropenia (D-VRd: 63.6%; VRd: 40.2%).

TEAEs reported in at least 20% of participants that occurred at ≥10.0% higher frequency in the D VRd treatment group compared with the VRd treatment group were pyrexia, chills, upper respiratory tract infection, diarrhoea, constipation, abdominal pain, paraesthesia, muscle spasms, neutropenia, leukopenia, cough, decreased appetite, and insomnia.

The only TEAE reported in at least 20% of participants that occurred at a ≥10.0% higher frequency in the VRd treatment group compared with the D-VRd treatment group was peripheral neuropathy. A difference of the same magnitude was not observed in the MMY3014 study were rates of peripheral neuropathy were comparable with 51.6% in the VRd arm in 53.6% in the D-VRd arm.

The incidence of Grade 3 or 4 TEAEs was higher in the D-VRd treatment group (85.9%) compared with the VRd treatment group (79.4%). The most frequently reported Grade 3 or 4 TEAEs (≥10.0% in either treatment group) were cytopenia TEAEs.

The most frequently reported daratumumab-related TEAEs (≥20%) in the D-VRd treatment group were neutropenia (47.5%), fatigue (38.4%), thrombocytopenia (29.3%), diarrhoea (28.3%), upper respiratory tract infection (27.3%), nausea (26.3%), anaemia (25.3%), leukopenia (23.2%), pyrexia (22.2%), and lymphopenia (21.2%).

In the PLEIADES study, the most frequently reported TEAEs (≥20%) were peripheral sensory neuropathy (41.8%), thrombocytopenia (38.8%), constipation (38.8%), neutropenia (37.3%), pyrexia (35.8%), fatigue (28.4%), and diarrhoea (23.9%).

Adverse drug reactions

The MAH evaluated safety data using the definition of ADR from the International Council for Harmonisation guideline entitled, E6: Good Clinical Practice, Consolidated Guideline.

ADRs in Study MMY3014 were evaluated according to the following criteria:

- All TEAEs reported in ≥10% of participants and occurred at a higher incidence (≥5% difference) in the D-VRd arm as compared with the VRd arm were considered to have met the ADR threshold. The comparison of incidence of TEAEs between treatment arms was completed after rounding incidence to the nearest whole numbers for all events (i.e., 4.9% is rounded to 5%).
- All laboratory parameters in Study MMY3014 were reviewed. No laboratory parameters had an incidence of Grade 3 or 4 values ≥10% except for haematology parameters.
- Thrombocytopenia, Neutropenia, Lymphopenia, Leukopenia, and Anaemia were listed in a separate haematology laboratory table based on haematology laboratory parameters regardless of the incidence and difference between arms.
- SAEs that occurred at a higher incidence (≥2% difference) in the D-VRd treatment arm as compared with the VRd treatment arm were considered ADRs. The comparison of incidence was completed after rounding incidence to whole numbers for all events.
- TEAEs were evaluated in the context of a potential plausible biological or pharmacological association with daratumumab or as medically significant events with a high probability that they could be associated with daratumumab, regardless of frequency.

Based on this analysis, no new ADRs were identified from Study MMY3014. The frequency of the known ADRs associated with daratumumab use were updated with data from the MMY3014 and the PLEIADES study which were combined with other daratumumab monotherapy and combination studies to obtain ADR frequencies from a pooled safety data (Table 22).

Table 22. Adverse Reactions in Multiple Myeloma and AL Amyloidosis Participants Treated With Daratumumab IV or Daratumumab SC (pooled data from **MMY3014 and the PLEIADES studies**)

	Any Grades	Any Grades	Grade 3-4
Infections and infestations			
Upper respiratory tract infection[a]	Very Common	39%	2%
COVID-19[a,g]	Very Common	38%	7%
Pneumonia[a]	Very Common	18%	11%
Bronchitis[a]	Very Common	14%	1%
Urinary tract infection	Common	7%	1%
Influenza	Common	4%	1%[#]
Sepsis[a]	Common	4%	4%
Cytomegalovirus infection[a]	Uncommon	<1%	<1%[#]
Hepatitis B reactivation[a]	Uncommon	<1%	<1%
Blood and lymphatic system disorders			
Neutropenia[a]	Very Common	43%	37%
Thrombocytopenia[a]	Very Common	31%	18%
Anaemia[a]	Very Common	27%	11%
Lymphopenia[a]	Very Common	13%	10%
Leukopenia[a]	Very Common	11%	6%
Immune system disorders			
Anaphylactic reaction[b]	Rare		
Hypogammaglobulinaemia[a]	Common	3%	<1%[#]
Metabolism and nutrition disorders			
Decreased appetite	Very Common	10%	<1%
Hyperglycaemia	Common	6%	3%
Hypocalcaemia	Common	6%	1%
Dehydration	Common	2%	1%[#]
Psychiatric disorders			
Insomnia	Very Common	16%	1%[#]
Nervous system disorders			
Peripheral sensory neuropathy	Very Common	29%	3%
Headache	Very Common	10%	<1%[#]
Dizziness	Common	9%	<1%[#]
Paraesthesia	Common	9%	<1%
Syncope	Common	3%	2%[#]
Cardiac disorders			
Atrial fibrillation	Common	3%	1%
Vascular disorders			
Hypertension[a]	Common	9%	4%
Respiratory, thoracic and mediastinal disorders			
Cough[a]	Very Common	22%	<1%[#]
Dyspnoea[a]	Very Common	18%	2%
Pulmonary oedema[a]	Common	1%	<1%
Gastrointestinal disorders			
Diarrhoea	Very Common	32%	4%
Constipation	Very Common	28%	1%
Nausea	Very Common	22%	1%[#]
Vomiting	Very Common	13%	1%[#]
Pancreatitis[a]	Common	1%	<1%
Skin and subcutaneous tissue disorders			
Rash	Very Common	12%	1%[#]
Pruritus	Common	6%	<1%[#]
Musculoskeletal and connective tissue disorders			

	Any Grades	Any Grades	Grade 3-4
Back pain	Very Common	17%	2%
Arthralgia	Very Common	13%	1%
Muscle spasms	Very Common	12%	<1%[#]
Musculoskeletal chest pain	Common	6%	<1%[#]
General disorders and administration site conditions			
Fatigue	Very Common	23%	3%
Oedema peripheral[a]	Very Common	23%	1%
Pyrexia	Very Common	22%	1%
Asthenia	Very Common	19%	2%
Chills	Common	8%	<1%[#]
Injection site reactions[d,f]	Common	7%	0
Injury, poisoning and procedural complications			
Infusion related reactions[c]			
Daratumumab IV[e]	Very Common	39%	5%
Daratumumab SC[f]	Common	8%	1%

[#] No Grade 4.
[a] Indicates a grouping of terms.
[b] Based on postmarketing adverse reactions.
[c] Infusion related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
[d] Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
[e] Frequency based on daratumumab IV studies only (N=2324).
[f] Frequency based on daratumumab SC studies only (N=1183).
[g] Frequency based on MMY3014 study only (N=351) due to the onset of the pandemic during the study.
Note: Based on 3507 multiple myeloma and AL amyloidosis patients treated with daratumumab IV or daratumumab SC (daratumumab + rHuPH20).
Note: Studies included are AMY3001, MMY1001, MMY1002, MMY1004, MMY1008, MMY2002, MMY2040, MMY3003, MMY3004, MMY3006, MMY3007, MMY3008, MMY3012, MMY3013, MMY3014, GEN501, GEN503

Serious adverse event/deaths

Serious Adverse Events and Serious Adverse Events reported in participants with at least a 2% greater frequency in D-VRd than VRd in Study MMY3014 are summarised in **Table** 23 and **Table** 24 respectively.

Table 23. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (at Least 2% in Either VRd or D-VRd); Safety Analysis Set (Study MMY3014)

	VRd	D-VRd
Analysis set: safety	347	351
Total number of subjects with serious TEAE	171 (49.3%)	200 (57.0%)
MedDRA System Organ Class / Preferred Term		
Infections and infestations	95 (27.4%)	123 (35.0%)
Pneumonia	21 (6.1%)	40 (11.4%)
COVID-19	6 (1.7%)	13 (3.7%)
COVID-19 pneumonia	5 (1.4%)	11 (3.1%)
Lower respiratory tract infection	3 (0.9%)	9 (2.6%)
Sepsis	9 (2.6%)	7 (2.0%)
Upper respiratory tract infection	8 (2.3%)	7 (2.0%)
Blood and lymphatic system disorders	18 (5.2%)	24 (6.8%)
Febrile neutropenia	16 (4.6%)	16 (4.6%)
Gastrointestinal disorders	23 (6.6%)	23 (6.6%)
Diarrhoea	9 (2.6%)	7 (2.0%)
Respiratory, thoracic and mediastinal disorders	12 (3.5%)	23 (6.6%)
Pulmonary embolism	5 (1.4%)	9 (2.6%)

	VRd	D-VRd
Cardiac disorders	12 (3.5%)	21 (6.0%)
Atrial fibrillation	2 (0.6%)	9 (2.6%)
Nervous system disorders	13 (3.7%)	19 (5.4%)
General disorders and administration site conditions	21 (6.1%)	17 (4.8%)
Pyrexia	16 (4.6%)	13 (3.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (3.7%)	15 (4.3%)
Injury, poisoning and procedural complications	12 (3.5%)	13 (3.7%)
Vascular disorders	10 (2.9%)	13 (3.7%)
Hepatobiliary disorders	4 (1.2%)	12 (3.4%)
Musculoskeletal and connective tissue disorders	7 (2.0%)	10 (2.8%)
Metabolism and nutrition disorders	10 (2.9%)	8 (2.3%)

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.
Key: TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Percentages are calculated with the number of subjects in each group as denominator.
Note: Adverse events are coded using MedDRA version 26.0.

Table 24. Serious Adverse Events Reported in Participants With at Least a 2% Greater Frequency in D-VRd than VRd (Study MMY3014)

	VRd				D-VRd			
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
Analysis set: safety	347				351			
Infections and infestations								
Pneumonia[a]	27 (10.0%)	20 (7.5%)	2 (0.6%)	2 (0.6%)	57 (20.3%)	45 (16.2%)	3 (0.9%)	0
COVID-19[b]	10 (3.7%)	0	0	0	23 (8.2%)	0	0	0
Cardiac disorders								
Atrial fibrillation	2 (0.7%)	1 (0.4%)	1 (0.3%)	0	9 (3.2%)	6 (2.2%)	1 (0.3%)	0

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone

[a] Pneumonia includes atypical pneumonia, bronchopneumonia, bronchopulmonary aspergillosis, idiopathic interstitial pneumonia, lobar pneumonia, lower respiratory tract infection, lung infection, pneumocystis jirovecii infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia haemophilus, pneumonia influenzal, pneumonia klebsiella, pneumonia legionella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia staphylococcal, pneumonia streptococcal, pneumonia viral, and pulmonary mycosis.

[b] COVID-19 includes COVID-19, and COVID-19 pneumonia.

Note: Denominator is based on the number of randomized subjects in the safety analysis set. A 2% difference is determined by first rounding to the nearest whole number (the convention used for ADR determination).
Adverse events are reported using MedDRA version 26.0

The incidence of treatment-emergent SAEs was lower in the D-VRd treatment group (46.5%) compared with the VRd treatment group (52.0%) in the GRIFFIN study. The most common (≥5%) treatment emergent SAEs in the D-VRd and VRd treatment groups, respectively, were Pneumonia (15.2%; 13.7%) and Pyrexia (11.1%; 9.8%).

Treatment-emergent SAEs were reported in 28.4% of participants in the D VRd cohort of the PLEIADES study. The only treatment-emergent SAE reported by ≥5% of participants was Pyrexia in the D VRd cohort (6.0%).

Deaths

At the time of the CCO (01 August 2023), a total of 34 (9.7%) participants in the D-VRd arm and 43 (12.4%) participants in the VRd arm of the safety analysis set in Study MMY3014 had died. An additional participant in the VRd arm died prior to receiving study treatment and therefore was not included in the safety analysis set but was included in the ITT analysis set used for OS analysis. The primary causes of death were either disease progression (D-VRd: 4.6%; VRd: 5.5%) or AEs (D-VRd: 4.3%; VRd: 5.5%). The latter included 5 deaths due to COVID-19 AEs (D-VRd: 4 [1.1%]; VRd: 1 [0.3%]). In addition, there were 2 deaths due to COVID-19 in the VRd arm classified under Other causes, because these events occurred outside of the TEAE reporting period. Of the 34 total deaths due to AEs, 29 were due to TEAEs and 5 were due to serious events not classified as TEAEs as they occurred outside of the TEAE reporting period.

The proportion of participants who died within 30 days of the last dose of study treatment was lower in the D-VRd arm compared with the VRd arm (D-VRd: 2.6%; VRd: 4.0%). Early deaths (occurring within 60 days of the first treatment) were reported for 1 (0.3%) participant in the D-VRd arm and 4 (1.2%) participants in the VRd arm. The primary causes of all 5 early deaths were AEs.

TEAEs with an outcome of death were similar in both treatment arms (D-VRd: 3.7%; VRd: 4.6%). TEAEs with an outcome of death reported for ≥2 participants were COVID 19, COVID-19 pneumonia, and Sepsis (2 [0.6%] each) in the D-VRd arm, and Sepsis and Septic shock (3 [0.9%] each), and Cardiac arrest and Myocardial infarction (2 [0.6%] each) in the VRd arm.

In the GRIFFIN study, a total of 14 (7%) randomised participants died (D-VRd: 7 [7.1%]; VRd: 7 [6.9%]). In the D-VRd treatment group, 5 (5.1%) participants died due to PD after treatment discontinuation, 1 (1%) participant died due to a TEAE of Pneumonia (bronchopneumonia), and 1 (1%) participant died outside the TEAE reporting period. In the VRd treatment group, 4 (3.9%) participants died due to PD after treatment discontinuation, 1 (1%) participant had a TEAE of death of unknown cause, and 2 (2.0%) participants died outside the TEAE reporting period.

One (1.5%) participant in the D-VRd cohort of the PLEIADES study died due to a TEAE of Respiratory failure considered unrelated to treatment.

Laboratory findings

Haematological abnormalities were reported for most participants in Study MMY3014, consistent with the incidence of TEAEs in the SOC of Blood and Lymphatic Disorders. Grade 3 and 4 haematology values (i.e., low WBC, low platelets, low neutrophils, low lymphocytes, and low haemoglobin) were reported at higher rates in the D-VRd arm compared with the VRd arm.

The most common Grade 3 or 4 hematologic abnormalities for both treatment arms were low neutrophils and low lymphocytes. There were no Grade 4 low haemoglobin values reported in either treatment arm.

Overall, the chemistry values were consistent between treatment arms. There were no Grade 3 or 4 chemistry laboratory abnormalities reported at a frequency >10% in either treatment arm.

Safety in special populations

Adverse events analysis by age group is summarised in **Table 25.**

Table 25. Summary of adverse events by age group (Study MMY3014)

MedDRA Terms	**Age <50** number (%) N = 53	**Age 50 - <65** number (%) N = 205	**Age 65+** number (%) N= 93
Total AEs	52 (98.1%)	204 (99.5%)	93 (100.0%)
Serious AEs – Total	23 (43.4%)	112 (54.6%)	65 (69.9%)
Fatal	0	8 (3.9%)	5 (5.4%)
Hospitalization/prolong existing hospitalization	20 (37.7%)	109 (53.2%)	59 (63.4%)
Life-threatening	1 (1.9%)	16 (7.8%)	12 (12.9%)
Disability/incapacity	0	0	1(1.1%)
Other (medically significant)	3 (5.7%)	18 (8.8%)	12 (12.9%)
AEs leading to drop-out[a]	2 (3.8%)	17 (8.3%)	12 (12.9%)
Psychiatric disorders	19 (35.8%)	78 (38.0%)	35 (37.6%)
Nervous system disorders	32 (60.4%)	151 (73.7%)	79 (84.9%)
Accidents and injuries[b]	9 (17.0%)	36 (17.6%)	19 (20.4%)
Cardiac disorders	5 (9.4%)	37 (18.0%)	18 (19.4%)
Vascular disorders	7 (13.2%)	55 (26.8%)	38 (40.9%)
Cerebrovascular disorders[c]	0	6 (2.9%)	3 (3.2%)
Infections and infestations	43 (81.1%)	180 (87.8%)	82 (88.2%)
Anticholinergic syndrome[d]	0	0	0
Quality of life decreased[e]	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	6 (11.3%)	39 (19.0%)	29 (31.2%)
Orthostatic hypotension	0	2 (1.0%)	5 (5.4%)
Falls	1 (1.9%)	4 (2.0%)	3 (3.2%)
Loss of consciousness/Syncope	2 (3.8%)	4 (2.0%)	7 (7.5%)
Dizziness[f]	0	17 (8.3%)	11 (11.8%)
Ataxia[g]	0	0	1 (1.1%)
Fractures	4 (7.5%)	23 (11.2%)	9 (9.7%)
<other AE appearing more frequently in older patients>[h]			
Bronchitis	8 (15.1%)	38 (18.5%)	22 (23.7%)
Neutropenia	31 (58.5%)	149 (72.7%)	63 (67.7%)
Thrombocytopenia	19 (35.8%)	99 (48.3%)	52 (55.9%)
Anaemia	7 (13.2%)	50 (24.4%)	21 (22.6%)
Diarrhoea	27 (50.9%)	134 (65.4%)	53 (57.0%)
Constipation	11 (20.8%)	64 (31.2%)	44 (47.3%)
Nausea	8 (15.1%)	39 (19.0%)	24 (25.8%)
Vomiting	2 (3.8%)	21 (10.2%)	15 (16.1%)
Abdominal pain	2 (3.8%)	16 (7.8%)	13 (14.0%)
Asthenia	10 (18.9%)	61 (29.8%)	23 (24.7%)
Oedema peripheral	4 (7.5%)	37 (18.0%)	31 (33.3%)
Peripheral sensory neuropathy	23 (43.4%)	111 (54.1%)	54 (58.1%)
Paraesthesia	4 (7.5%)	29 (14.1%)	13 (14.0%)
Dizziness	0	17 (8.3%)	10 (10.8%)
Back pain	7 (13.2%)	45 (22.0%)	28 (30.1%)
Muscle spasms	6 (11.3%)	41 (20.0%)	20 (21.5%)
Arthralgia	6 (11.3%)	38 (18.5%)	18 (19.4%)
Pain in extremity	7 (13.2%)	17 (8.3%)	16 (17.2%)
Rash	12 (22.6%)	44 (21.5%)	26 (28.0%)
Pruritus	3 (5.7%)	13 (6.3%)	10 (10.8%)
Dyspnoea	4 (7.5%)	20 (9.8%)	13 (14.0%)

MedDRA Terms	Age <50 number (%) N = 53	Age 50 - <65 number (%) N = 205	Age 65+ number (%) N= 93
Decreased appetite	0	20 (9.8%)	10 (10.8%)
Alanine aminotransferase increased	14 (26.4%)	26 (12.7%)	17 (18.3%)
Aspartate aminotransferase increased	8 (15.1%)	10 (4.9%)	10 (10.8%)
Hypertension	3 (5.7%)	16 (7.8%)	11 (11.8%)
Cataract	0	6 (2.9%)	10 (10.8%)

Key: AE=adverse event; MedDRA=medical dictionary for regulatory activities; TEAE=treatment-emergent adverse event

[a] AEs leading to study treatment discontinuation

[b] Accidents and injuries = SMQ Accident and Injuries narrow scope term

[c] Cerebrovascular disorders = SMQ central nervous system vascular disorders narrow scope terms

[d] Anticholinergic syndrome = SMQ anticholinergic syndrome narrow scope terms

[e] Includes the PTs: impaired quality of life; quality of life decreased

[f] Includes the PTs: dizziness/dizziness postural/dizziness exertional/persistent postural-perceptual dizziness

[g] Includes the PTs: ataxia/autoimmune cerebellar ataxia/cerebral ataxia/vestibular ataxia

[h] Defined as PTs with incidence ≥10% in age >65 subgroup in D-VRd arm and ≥5% higher than either of the other age subgroups

Sex

The overall incidence of TEAEs was comparable between male and female participants in both treatment arms in study MMY3014. The incidence of Grade 3 or 4 TEAEs was higher in females compared with males in both treatment arms (D-VRd: males, 89.5%; females, 94.4%; VRd: males, 84.7%; females, 86.9%). The incidence of SAEs was higher in males compared with females in both treatment arms (D-VRd: males, 59.3%; females, 53.5%; VRd: males, 54.0%; females, 42.8%).

Race

Interpretation of the subgroup analysis by race is limited due to the small number of enrolled participants from racial groups other than white in study MMY3014.

Renal Function

Interpretation of the subgroup analysis by baseline renal function is limited due to the small number of participants enrolled in the <60 mL/min subgroup compared with the 60 to <90 mL/min and ≥90 mL/min subgroups in both treatment arms.

There was a higher incidence of SAEs in the <60 mL/min subgroup compared with the other subgroups in both treatment arms (D-VRd: <60 mL/min, 74.2%; 60 to <90 mL/min, 53.4%; ≥90 mL/min, 56.9%; VRd: <60 mL/min, 55.6%; 60 to <90 mL/min, 43.9%; ≥90 mL/min, 52.5%).

Hepatic Function

Interpretation of the subgroup analysis by baseline hepatic function is limited due to the small number of participants with impaired hepatic function enrolled in the study.

Body Weight

The overall incidence of TEAEs was comparable across the weight subgroups for both treatment arms. Participants in the lowest body weight subgroup (≤65 kg) had a higher incidence of Neutropenia and Febrile neutropenia compared with the other subgroups in the D-VRd arm. In the VRd arm, the incidence of Neutropenia and Febrile neutropenia was higher in the >65 to 85 kg and >85 kg body

weight subgroups, respectively, compared with the other subgroups. However, the incidences of Infections and Infestations, including overall TEAEs, Grade 3 or 4 TEAEs, and SAEs were lower.

Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interaction studies were performed for daratumumab SC.

Discontinuation due to adverse events

Adverse Events Leading to Discontinuation of All Study Treatment

Table 26. Treatment-emergent Adverse Events Leading to All Treatment Discontinuation by System Organ Class, Preferred Term and Grade 3 or 4; Safety Analysis Set (Study MMY3014)

	VRd		D-VRd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Analysis set: safety	347		351	
Total number of subjects with TEAE leading to all treatment discontinuation[a]	74 (21.3%)	40 (11.5%)	31 (8.8%)	29 (8.3%)
MedDRA System Organ Class/ Preferred Term				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11 (3.2%)**	**10 (2.9%)**	**12 (3.4%)**	**12 (3.4%)**
Myelodysplastic syndrome	2 (0.6%)	2 (0.6%)	4 (1.1%)	4 (1.1%)
Acute myeloid leukaemia	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)
Acute lymphocytic leukaemia	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Angioimmunoblastic T-cell lymphoma	0	0	1 (0.3%)	1 (0.3%)
Cutaneous T-cell lymphoma	0	0	1 (0.3%)	1 (0.3%)
Prostate cancer	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Rectal adenocarcinoma	0	0	1 (0.3%)	1 (0.3%)
Squamous cell carcinoma	0	0	1 (0.3%)	1 (0.3%)
Adenocarcinoma of colon	1 (0.3%)	1 (0.3%)	0	0
Breast neoplasm	1 (0.3%)	1 (0.3%)	0	0
Malignant melanoma	1 (0.3%)	1 (0.3%)	0	0
Phaeochromocytoma	1 (0.3%)	1 (0.3%)	0	0
Infections and infestations	**7 (2.0%)**	**2 (0.6%)**	**8 (2.3%)**	**6 (1.7%)**
COVID-19 pneumonia	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Clostridium difficile colitis	0	0	1 (0.3%)	0
Pneumonia	4 (1.2%)	0	1 (0.3%)	1 (0.3%)
Pneumonia legionella	0	0	1 (0.3%)	1 (0.3%)
Pneumonia pneumococcal	0	0	1 (0.3%)	0
Sepsis	0	0	1 (0.3%)	1 (0.3%)
Septic shock	0	0	1 (0.3%)	1 (0.3%)
Urosepsis	0	0	1 (0.3%)	1 (0.3%)
COVID-19	1 (0.3%)	0	0	0
Infection	1 (0.3%)	0	0	0
Meningitis cryptococcal	1 (0.3%)	1 (0.3%)	0	0
General disorders and administration site conditions	**6 (1.7%)**	**1 (0.3%)**	**5 (1.4%)**	**2 (0.6%)**
Asthenia	0	0	3 (0.9%)	0
Fatigue	3 (0.9%)	0	1 (0.3%)	1 (0.3%)
General physical health deterioration	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Generalised oedema	1 (0.3%)	0	0	0
Malaise	1 (0.3%)	0	0	0

	VRd		D-VRd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Nervous system disorders	**12 (3.5%)**	**2 (0.6%)**	**5 (1.4%)**	**3 (0.9%)**
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	1 (0.3%)	1 (0.3%)
Headache	0	0	1 (0.3%)	0
Hypoxic-ischaemic encephalopathy	0	0	1 (0.3%)	0
Intensive care unit acquired weakness	0	0	1 (0.3%)	1 (0.3%)
Subarachnoid haemorrhage	0	0	1 (0.3%)	1 (0.3%)
Cerebrovascular accident	1 (0.3%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	1 (0.3%)	0	0
Neuralgia	1 (0.3%)	0	0	0
Neuropathy peripheral	1 (0.3%)	0	0	0
Peripheral motor neuropathy	2 (0.6%)	0	0	0
Peripheral sensory neuropathy	6 (1.7%)	1 (0.3%)	0	0
Blood and lymphatic system disorders	**14 (4.0%)**	**10 (2.9%)**	**2 (0.6%)**	**2 (0.6%)**
Thrombocytopenia	6 (1.7%)	4 (1.2%)	2 (0.6%)	2 (0.6%)
Anaemia	2 (0.6%)	1 (0.3%)	0	0
Febrile neutropenia	1 (0.3%)	1 (0.3%)	0	0
Immune thrombocytopenia	1 (0.3%)	1 (0.3%)	0	0
Leukopenia	1 (0.3%)	1 (0.3%)	0	0
Neutropenia	9 (2.6%)	7 (2.0%)	0	0
Metabolism and nutrition disorders	**1 (0.3%)**	**1 (0.3%)**	**2 (0.6%)**	**0**
Decreased appetite	0	0	2 (0.6%)	0
Hypoglycaemia	1 (0.3%)	1 (0.3%)	0	0
Musculoskeletal and connective tissue disorders	**2 (0.6%)**	**0**	**2 (0.6%)**	**2 (0.6%)**
Muscular weakness	0	0	1 (0.3%)	1 (0.3%)
Soft tissue necrosis	0	0	1 (0.3%)	1 (0.3%)
Muscle spasms	2 (0.6%)	0	0	0
Vascular disorders	**2 (0.6%)**	**1 (0.3%)**	**2 (0.6%)**	**1 (0.3%)**
Deep vein thrombosis	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Vasculitis	0	0	1 (0.3%)	1 (0.3%)
Hot flush	1 (0.3%)	0	0	0
Gastrointestinal disorders	**9 (2.6%)**	**3 (0.9%)**	**1 (0.3%)**	**1 (0.3%)**
Colitis	0	0	1 (0.3%)	1 (0.3%)
Diarrhoea	8 (2.3%)	3 (0.9%)	0	0
Gastrointestinal toxicity	1 (0.3%)	0	0	0
Injury, poisoning and procedural complications	**0**	**0**	**1 (0.3%)**	**1 (0.3%)**
Femur fracture	0	0	1 (0.3%)	1 (0.3%)
Psychiatric disorders	**0**	**0**	**1 (0.3%)**	**0**
Depressive symptom	0	0	1 (0.3%)	0
Renal and urinary disorders	**1 (0.3%)**	**1 (0.3%)**	**1 (0.3%)**	**1 (0.3%)**
Acute kidney injury	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Skin and subcutaneous tissue disorders	**4 (1.2%)**	**3 (0.9%)**	**1 (0.3%)**	**1 (0.3%)**
Toxic skin eruption	0	0	1 (0.3%)	1 (0.3%)
Eczema	1 (0.3%)	1 (0.3%)	0	0
Rash maculo-papular	1 (0.3%)	0	0	0
Stevens-Johnson syndrome	1 (0.3%)	1 (0.3%)	0	0
Urticaria	1 (0.3%)	1 (0.3%)	0	0
Cardiac disorders	**3 (0.9%)**	**2 (0.6%)**	**0**	**0**
Cardiac amyloidosis	1 (0.3%)	0	0	0
Cardiac failure	1 (0.3%)	1 (0.3%)	0	0
Myocardial infarction	1 (0.3%)	1 (0.3%)	0	0
Hepatobiliary disorders	**1 (0.3%)**	**1 (0.3%)**	**0**	**0**

	VRd		D-VRd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hepatotoxicity	1 (0.3%)	1 (0.3%)	0	0
Immune system disorders	**1 (0.3%)**	**0**	**0**	**0**
Drug hypersensitivity	1 (0.3%)	0	0	0
Investigations	**1 (0.3%)**	**0**	**0**	**0**
Alanine aminotransferase increased	1 (0.3%)	0	0	0
Respiratory, thoracic and mediastinal disorders	**4 (1.2%)**	**3 (0.9%)**	**0**	**0**
Interstitial lung disease	1 (0.3%)	1 (0.3%)	0	0
Lung disorder	1 (0.3%)	0	0	0
Pneumonitis	1 (0.3%)	1 (0.3%)	0	0
Pulmonary embolism	1 (0.3%)	1 (0.3%)	0	0

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone.
Key: TEAE = treatment-emergent adverse event.
[a] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Percentages are calculated with the number of subjects in each group as denominator.
Note: Adverse events are coded using MedDRA version 26.0.

Adverse Events Leading to Discontinuation of Any Component of Study Treatment

The rate of TEAEs leading to discontinuation of *any* component of study treatment (i.e., daratumumab, bortezomib, lenalidomide, or dexamethasone) was similar in both treatment arms (D-VRd: 33.0%; VRd: 30.0%).

The most common TEAEs leading to discontinuation of any component of study treatment with a frequency ≥2% in either treatment arm were:

- Peripheral sensory neuropathy (D-VRd: 7.1%; VRd: 6.9%)
- Diarrhoea (D-VRd: 4.0%; VRd: 2.6%)
- Neutropenia (D-VRd: 2.3%; VRd: 3.5%)
- Thrombocytopenia (D-VRd: 2.3%; VRd: 2.0%)
- Asthenia (D-VRd: 2.0%; VRd: 0%)

The rate of TEAEs leading to discontinuation of daratumumab was 9.7% (34/351). This included 8.5% of participants with Grade 3 or 4 TEAEs. TEAEs resulting in discontinuation of daratumumab which occurred in >2 participants were Thrombocytopenia (3 [0.9%]) and COVID 19 pneumonia (4 [1.1%]).

The majority of TEAEs leading to discontinuation of daratumumab occurred during maintenance (25 out of 34 discontinuations).

The rate of TEAEs leading to discontinuation of bortezomib was similar in both treatment arms (D-VRd: 12.3%; VRd: 11.8%). The majority of TEAEs leading to discontinuation of bortezomib occurred during induction in both treatment arms.

The rate of TEAEs leading to discontinuation of lenalidomide was high in both treatment arms (D-VRd: 27.1% (95/351); VRd: 23.3% (81/347)). The majority of TEAEs leading to discontinuation of lenalidomide occurred during maintenance in both treatment arms.

The rate of TEAEs leading to discontinuation of dexamethasone was similar in both treatment arms (D-VRd: 4.8%; VRd: 6.3%).

The incidence of TEAEs leading to study treatment discontinuation (i.e., any component of study treatment) was similar between the D-VRd treatment group (29.3%) and the VRd treatment group (29.4%) in the GRIFFIN study. Most of the TEAEs that resulted in study treatment discontinuation were Grade 1 or 2. In the D-VRd treatment group, TEAEs that resulted in discontinuation of >1 participant were Peripheral sensory neuropathy (11.1%), Neuralgia (4.0%), and Neuropathy peripheral, Neutropenia, and Rash (2.0% each).

The incidence of TEAEs leading to discontinuation of any component of study treatment (i.e., daratumumab SC, bortezomib, lenalidomide, dexamethasone/corticosteroids) in the D-VRd cohort in the PLEIADES study was 11.9%. The only TEAEs leading to discontinuation of any component occurring in >1 participant was Peripheral sensory neuropathy (D-VRd: 6.0%). TEAEs leading to daratumumab SC treatment discontinuation occurred in 2 participants (3.0%). Of these, 1 participant (1.5%) had a Grade 3 or 4 event. There were no TEAEs leading to discontinuation of daratumumab SC occurring in >1 participant.

Post marketing experience

Post-marketing safety information is available for both daratumumab SC and daratumumab IV.

A cumulative review was performed for all medically confirmed spontaneous cases (serious and nonserious) of daratumumab received in the Global Medical Safety (GMS) database through 01 August 2023. A separate cumulative review of cases reporting SC administration was also performed.

Based on 4,516,014,540 mg distributed worldwide by the MAH from launch to 31 July 2023, the estimated exposure to daratumumab IV is 177,790 person-years.

Based on 5,900,450,400 mg distributed worldwide by the MAH from launch to 31 July 2023, the estimated exposure to daratumumab SC is 149,001 person-years.

Based on the total 10,416,464,940 mg distributed worldwide by the MAH from launch to 31 July 2023, the estimated exposure to daratumumab IV and SC is 326,791 person-years.

The cumulative search of the GMS database through 01 August 2023 retrieved a total of 15,531 spontaneous cases. Of these, 1,763 cases were screened as medically unconfirmed cases (1,117) and cases reporting multiple unidentifiable patients (646), therefore resulting in 13,768 spontaneous cases for further analysis. Of the 13,768 cases, for the cases reporting sex, more than half of the cases (55%, 4,695/8,542) concerned males and where age or age group was reported, most concerned elderly patients (60.2%; 4,863/8,084). The patients' age ranged from 0.1 to 100 years (mean age was 66 years, and the median age was 68 years).

Of the 13,768 cases, the most frequently reported MedDRA SOCs were Injury, poisoning and procedural complications (30.5%), General disorders and administration site conditions (14.2%), Respiratory, thoracic, and mediastinal disorders (8.3%), Investigations (6.8%), and Infections and Infestations (6.3%). The most common PTs were Off label use (8.6%), Infusion related reaction (8.1%), and Intentional product use issue (3.3%). Of the 13,768 cases, 1,918 (13.9%) reported daratumumab SC administration. Injury, poisoning and procedural complications (24.8%), General disorders and administration site conditions (17.3%), and Investigations (7.2%) were the most common SOCs. Off label use (7.2%), Intentional product use issue (4.2%), and Infusion related reaction (3.1%) were the most common PTs.

Of the 13,768 cases, 7,018 were serious. Among these serious cases, the most frequently reported serious PTs (≥ 2% of the reported events) were Plasma cell myeloma (7.4%), Infusion related reaction (7.3%), Death (3.2%), Disease progression and Neutropenia (3.1% each), Pneumonia (2.6%), Thrombocytopenia (2.4%), and Dyspnoea (2.1%). Of the 7,018 serious cases, 768 (10.9%) reported daratumumab SC administration. The most frequently reported serious PTs (≥ 2% of the reported events) involving SC administration of daratumumab were Neutropenia and Plasma cell myeloma (5.1% each), Thrombocytopenia (3.0%), Infusion related reaction (2.8%), and Pneumonia (2.6%).

A total of 1,047 cases reported 1,326 events with a fatal outcome. Among these cases, the most frequently reported fatal PTs (≥2% of the reported events) were Death (28.7%), Plasma cell myeloma (9.4%), Disease progression (6.9%), Pneumonia (3.5%), Sepsis (3.5%), COVID-19 (2.9%), and Septic shock (2.3%). Of the 1,047 cases reporting fatal events, 63 (6.0%) reported daratumumab SC administration. Among these 63 cases, the most frequently reported fatal PTs (≥2% of the reported events) were Death (26.5%), Plasma cell myeloma (9.6%), Septic shock (7.2%), Cardio-respiratory arrest and Infusion related reaction (3.6% each), and Cardiac failure, COVID-19, COVID-19 pneumonia, Primary amyloidosis, and Sepsis (2.4% each).

2.5.1. Discussion on clinical safety

The safety profile of daratumumab in combination with bortezomib, lenalidomide and dexamethasone in patients with NDMM eligible for ASCT is based on the results from the open-label, randomised, phase 3 study MMY3014. Supportive data from the phase 2 study GRIFFIN who received the same backbone treatment with a slightly different treatment schedule and intravenous administration of daratumumab have also been included. Additionally, safety data from the PLEIADES study where daratumumab was added to four cycles of VRd induction treatment have also been provided.

The adverse event profile of daratumumab in combination with VRd was consistent with the already known safety profile of daratumumab from previous clinical studies. No new ADRs were identified from the submitted data, however, the frequencies of a number of known ADRs, including that for COVID-19 have been updated.

The PT of pulmonary embolism occurred at a higher incidence in the D-VRd arm as compared with the VRd arm (2.6% vs. 1.4%). However, it is acknowledged that multiple myeloma in itself conveys an increased risk of VTEs and that VTEs are a well-established risk with lenalidomide treatment. Additional risk factors for VTEs in patients with multiple myeloma are immobilisation related to bone involvement, kidney injury, diabetes due to glucocorticoid use, and acute infection due to immunosuppression. COVID-19 also increases the risk of pulmonary embolism and this also occurred with a higher frequency in the D-VRd arm. Due to these confounding factors the CHMP considered that pulmonary embolism should not be considered a new ADR for daratumumab.

The most clinically important adverse events (all grades, preferred terms) that occurred more frequently reported in the D-VRd arm compared to the VRd arm in study MMY3014 were neutropenia (69.2% vs 58.8%), thrombocytopenia (48.4% vs. 34.3%), diarrhoea (61.0% vs 54.2%), Insomnia (27.1% vs. 17.6%)
and pneumonia (18.2% vs 11.0%). The addition of daratumumab to the VRd backbone and to lenalidomide maintenance led to increased rates of airway infections and symptoms, neutropenia, thrombocytopenia, diarrhoea and insomnia.

Focusing on maximum toxicity grade, the overall incidence of Grade 3 or 4 TEAEs was higher in the D-VRd arm compared with the VRd arm (91.5% vs. 85.6%) with largest differences between arms observed for neutropenia (62.1% vs. 51.0%) and thrombocytopenia (29.1% vs. 17.3%). No Grade 3 or 4 TEAEs occurred at a ≥5% higher frequency in the VRd arm compared with the D-VRd arm.

The incidence of treatment-emergent SAEs was higher in the D-VRd arm compared with the VRd arm (D-VRd: 57.0%; VRd: 49.3%), driven by a higher incidence of SAEs during maintenance in the D-VRd arm (D-VRd: 38.8%; VRd: 26.0%). The incidence of SAEs was similar in both treatment arms during induction and consolidation. The most common treatment-emergent SAEs at a ≥2% higher frequency in the D-VRd arm compared with the VRd arm were, Pneumonia (D-VRd: 11.4%; VRd: 6.1%), COVID-19 (D-VRd: 3.7%; VRd: 1.7%), and Atrial fibrillation (D-VRd: 2.6%; VRd: 0.6%). No treatment-emergent SAEs occurred at a ≥2% higher frequency in the VRd arm compared with the D-VRd arm.

A total of 34 participants (9.7%) in the D-VRd arm and 43 participants (12.4%) in the VRd arm had died at the time of the CCO (01 August 2023). The primary causes of death were either AEs (D-VRd: 4.3%;

VRd: 5.5%) or disease progression (D-VRd: 4.6%; VRd: 5.5%). Of note, deaths within 60 days of first study treatment were reported for 1 (0.3%) participant in the D-VRd arm and 4 (1.2%) participants in the VRd arm. The primary causes of all 5 early deaths were AEs. This suggests that adding daratumumab to VRd does not increase the risk of early death in the induction phase.

The rate of TEAEs leading to discontinuation of all study treatment was lower in the D-VRd arm compared with the VRd arm (D-VRd: 8.8%; VRd: 21.3%). This difference was driven by the higher incidence of TEAEs leading to discontinuation of study treatment (predominantly lenalidomide) during maintenance in the VRd arm (D-VRd: 7.1%; VRd: 19.0%). The participants in the VRd arm only received treatment with lenalidomide during maintenance therapy, thus any discontinuation of lenalidomide led to discontinuation of all study drugs. In contrast, in the D-VRd arm, if participants discontinued lenalidomide during maintenance therapy, daratumumab study treatment was not discontinued.

The rate of TEAEs leading to discontinuation of daratumumab was 9.7% (34/351). This included 8.5% of participants with Grade 3 or 4 TEAEs. TEAEs resulting in discontinuation of daratumumab which occurred in >2 participants were Thrombocytopenia (3 [0.9%]) and COVID-19 pneumonia (4 [1.1%]). The majority of TEAEs leading to discontinuation of daratumumab occurred during maintenance (25 out of 34 discontinuations).

The lack of drug-drug interaction studies for daratumumab was considered acceptable. As an IgG1κ monoclonal antibody, the biotransformation of daratumumab is expected to be similar to endogenous IgG (i.e., degraded into small peptides and amino acids via catabolic pathways) and subject to similar elimination pathways (Tabrizi 2006; Mascelli 2007). Renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are therefore unlikely to represent major elimination routes. Due to the high affinity to a unique epitope on cluster of differentiation 38, daratumumab is also not anticipated to alter the activity of drug-metabolizing enzymes. Since there is no overlapping pathway of elimination, no interactions are expected between daratumumab and small molecule drugs including bortezomib, lenalidomide and dexamethasone.

No new safety signals were identified from the cumulative review of post-marketing cases, both overall and separately for daratumumab SC. The cumulative review of the post-marketing spontaneous cases revealed that based on the most common events, SAEs, and fatal events, the post-marketing experience of daratumumab SC is generally consistent with the overall post-marketing experience. The post-marketing experience was consistent with the known safety profile of daratumumab or clinical experience of the population under treatment.

2.5.2. Conclusions on clinical safety

Safety findings from the pivotal study MMY3014 in support of this application and the supportive GRIFFIN and PLEIADES studies are consistent with the known safety profile of daratumumab as characterised previously from other clinical studies.

No new ADRs were identified but the frequency of some of these ADRs has been updated based on the totality of the data. Even though the addition of daratumumab to VRd resulted in slightly more grade 3 and 4 TEAEs and SAEs, this did not lead to more treatment related deaths.

Overall, submitted safety information supports the use of daratumumab in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 10.1 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
	Hepatitis B virus reactivation
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities				
A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Ongoing	Primary objective is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome.	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Draft Protocol: Interim report: Final report:	Aug 2021 2nd Quarter 2024 1st Quarter 2026

Risk minimisation measures

Summary Table of Risk Minimisation Activities

Safety Concern	Risk Minimization Measures
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: • SmPC Section 4.4, which advises that patients should be typed and screened, and phenotyping or genotyping be considered prior to starting daratumumab treatment; • SmPC Sections 4.4, which advises HCPs to notify blood transfusion centers of this interference with indirect antiglobulin tests in the event of a planned transfusion; • SmPC Section 4.4, which recommend that if an emergency transfusion is required, non-cross-matched ABO/RhD compatible RBCs can be given per local blood bank practices; • SmPC Section 4.5, which recommend mitigating daratumumab interference by treating reagent RBCs with DTT to disrupt daratumumab binding or other locally validated methods, and that Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT treated RBCs; • PL Section 2, which instructs patients to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab. Additional risk minimization measures: • Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in the PL, in Annex II, D.
Hepatitis B virus reactivation	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4; • SmPC Section 4.4 and PL Section 2, which advise HBV screening before initiation of treatment with daratumumab and to monitor for clinical and laboratory signs of HBV reactivation during and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology; • SmPC Section 4.4, which advises to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated; • SmPC Section 4.4, which advises to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV; • PL Section 2, which includes a warning to patients with history or current HBV infection; Additional risk minimization measures: • Distribution of a DHPC to HCPs who prescribe daratumumab was issued in the EU member states in June 2019.
Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Routine risk minimization measures: • SmPC Section 5.1. Additional risk minimization measures: • None.

Key: AL amyloidosis = light chain amyloidosis; DHPC = Direct Healthcare Professional Communication; DTT = dithiothreitol; HBC = hepatitis B virus; HCP = healthcare professional; PL = package leaflet; RBC = red blood cell; SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative in Ireland.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the currently proposed indication extension, minimal changes have been introduced to the package leaflet and the proposed changes reflect language and a format that is consistent with that in the currently approved leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH submitted a variation application to extend the indication of Darzalex 1800 mg solution for subcutaneous injection to include daratumumab in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

The proposed addition to the existing indication is only for the subcutaneous use of daratumumab.

3.1.2. Available therapies and unmet medical need

High-dose chemotherapy with melphalan followed by ASCT is the standard approach for eligible patients. Bortezomib, lenalidomide, and dexamethasone (VRd), along other triplet regimens such as bortezomib, thalidomide, and dexamethasone (VTd) and bortezomib, cyclophosphamide, and dexamethasone (VCd), are amongst the preferred induction regimens recommended by NCCN and ESMO treatment guidelines for the primary therapy of patients with NDMM who are candidates for transplantation.

After transplant, some patients are given a further short intense period of treatment to deepen the response obtained with induction therapy, commonly referred to as consolidation therapy. Maintenance therapy is generally administered for a long duration and aims to improve PFS with minimal toxicity and without impacting quality of life. Lenalidomide was approved in the US and Europe in 2017 as monotherapy for maintenance therapy and is currently considered the standard of care.

3.1.3. Main clinical studies

Study MMY3014 (PERSEUS) was a phase 3, randomised, open-label, multicentre study comparing D-VRd versus VRd in participants with newly diagnosed MM who were eligible for ASCT. The treatment phase included four elements: Induction treatment, ASCT, consolidation treatment, and maintenance treatment (DR vs. R).

The primary endpoint was PFS defined as time from the date of randomization to the date of PD (assessed by 2011 IMWG criteria) or death. The key secondary endpoints were overall CR or better rate anytime during the study, overall MRD-negativity rate (10^{-5}) achieved at any time during the study, and OS. Participants were randomised in a 1:1 ratio, stratified by ISS Stage I, II, or III disease (β-2 microglobulin and albumin) and cytogenetics (standard-risk or high-risk, which is defined by the presence of del17p, t[4;14] or t[14;16]).

3.2. Favourable effects

At the CCO of 01 August 2023, when the first planned interim analysis was conducted, a total of 153 PFS events (D-VRd: 50/355 (14.1%); VRd: 103/354 (29.1%)) had been observed, with a median follow-up of 47.51 months (D-VRd: 47.57 months; VRd: 47.38 months). The addition of daratumumab to VRd resulted in a statistically significant improvement in the primary endpoint PFS with a HR=0.42 (95% CI: 0.30, 0.59; 2-sided p <0.0001) compared to VRd alone.

The result for the primary endpoint was supported by the key secondary endpoints, overall CR or better rate and MRD-negativity at a 10^{-5} threshold. Both endpoints favoured D-VRd treatment over VRd treatment. With a total of 78 deaths (D-VRd: 34; VRd: 44), the median OS was not reached for either treatment arm.

3.3. Uncertainties and limitations about favourable effects

The PFS benefit was generally consistent across prespecified subgroups (ISS stage, cytogenetic risk, and baseline ECOG performance score), with the exception of the ≥65 years subgroup. However, there was an imbalance in the cytogenetic high-risk category (D-VRd 25.5% vs VRD 19.5%) in this subgroup, which may have contributed to the observed HR.

OS data are immature. In addition, it is unlikely that the trial will be able to demonstrate that the PFS benefit shown will translate into OS superiority, since it is likely that many patients randomised to the VRd arm will receive daratumumab in subsequent treatment lines, confounding OS.

The study design does not allow for evaluation of the treatment effect of adding daratumumab to VRd in the induction phase or consolidation phase or to lenalidomide in the maintenance phase respectively, as re-randomisation pre-consolidation or re-randomisation pre-maintenance were not considered. The treatment effect of adding daratumumab to the VRd backbone and to lenalidomide maintenance has to be considered across all treatment phases as a whole.

3.4. Unfavourable effects

The most clinically important adverse events (all grades, preferred terms) more frequently reported in the D-VRd arm compared to the VRd arm in study MMY3014 were neutropenia (69.2% vs 58.8%), thrombocytopenia (48.4% vs. 34.3%), diarrhoea (61.0% vs 54.2%), insomnia (27.1% vs. 17.6%) and pneumonia (18.2% vs 11.0%) consistent with the previous available data.

Focusing on maximum toxicity grade, the overall incidence of Grade 3 or 4 TEAEs was higher in the D-VRd arm compared with the VRd arm (91.5% vs. 85.6%) with largest differences between arms observed for neutropenia (62.1% vs. 51.0%) and thrombocytopenia (29.1% vs. 17.3%).

A total of 34 participants (9.7%) in the D-VRd arm and 43 participants (12.4%) in the VRd arm had died at the time of the CCO (01 August 2023). The primary causes of death were either AEs (D-VRd: 4.3%; VRd: 5.5%) or disease progression (D-VRd: 4.6%; VRd: 5.5%). Of note, deaths within 60 days of first study treatment were reported for 1 (0.3%) participant in the D-VRd arm and 4 (1.2%) participants in the VRd arm. The primary causes of all 5 early deaths were AEs.

3.5. Uncertainties and limitations about unfavourable effects

The median age of the included patients in the pivotal trial was 60 years, which is well below the average age of patients diagnosed with multiple myeloma (approximately 70 years). A screening period of 28 days before randomisation to treatment excluded patients with NDMM who needed acute or sub-acute anti-myeloma treatment with more than just 40mg x 4 of dexamethasone to alleviate kidney disease, severe hypercalcemia or significant bone disease. Given these selection criteria selecting for a fit, younger patient population with low symptom burden from multiple myeloma and low levels of comorbidity, it is likely that AE rates and complications to treatment will be higher outside clinical trial settings than what was observed in study MMY3014.

3.6. Effects Table

Table 27. Effects Table for Darzalex in combination with bortezomib, lenalidomide and dexamethasone for the treatment of NDMM in patients eligible for ASCT (data cut-off: 01 August 2023)

Effect	Short description	Unit	D-VRd n = 355	VRd n =354	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Time from randomisation to first disease progression (according to the IMWG response criteria) or death	N %	50 14.1%	103 29.1%	SoE: PFS: HR 0.42 (95% CI: 0.30, 0.59) CR or better rate: OR 3.13, (95% CI: 2.11, 4.65) MRD negativity $10^{-5:}$ OR: 3.40 (95% CI: 2.47, 4.69)	MMY3014
Unfavourable Effects			**D-VRd n = 351**	**VRd n = 347**		
Grade 5 AEs	AEs leading to death	%	4.3	5.5		MMY3014
Neutropenia	All Grade 3-4	% %	69.2 62.1	58.8 51.0		
Diarrhoea	All Grade 3-4	% %	61.0 10.5	54.2 7.8		
Thrombocytopenia	All Grade 3-4	% %	48.4 29.1	34.3 17.3		
Insomnia	All Grade 3-4	% %	27.1 2.3	17.6 1.7		
Pneumonia	All Grade 3-4	% %	18.2 10.5	11.0 6.1		

Abbreviations: D= daratumumab; VRd= bortezomib, lenalidomide and dexamethasone; PFS = Progression free survival; IMWG= International Myeloma Working Group; HR = Hazard ratio; CI = Confidence Interval, CR: Complete response; MRD: Minimal residual disease

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the interim analysis of study MMY3014 showed a statistically significant relevant improvement in PFS from the addition of daratumumab to VRd induction and consolidation treatment and from daratumumab added to lenalidomide maintenance treatment in patients with newly diagnosed multiple myeloma. This improvement is considered clinically significant and is supported by secondary endpoints such as statistically significant improvement in overall CR or better treatment response rates and statistically significant higher proportion of patients achieving MRD negativity at the 10^{-5} threshold. OS data are immature but do not show any sign of detriment in the experimental arm.

The safety profile is in general as expected in the context of the patient population, the backbone therapy and the known safety profile of daratumumab SC. Overall there are no new safety findings or new adverse drug reactions, although daratumumab may increase the risk for neutropenia, thrombocytopenia, pneumonia, diarrhoea and insomnia induced by backbone therapy. The overall incidence of Grade 3 or 4 AEs was higher in the D-VRd arm compared with the VRd arm with largest differences between arms observed for neutropenia and thrombocytopenia. The incidence of SAEs was higher in the D-VRd arm but were driven by a higher incidence of SAEs during the maintenance phase in the D-VRd arm. Deaths due to AEs were comparable between study arms.

3.7.2. Balance of benefits and risks

The combination of D-VRd has demonstrated to confer clinically relevant benefit in the treatment of adult patients with newly diagnosed multiple myeloma. This is considered to outweigh the toxicity of the combination, which is in line with the known safety profile of daratumumab and which can be managed adequately with the routine and additional risk minimisation measures that are already in place for this product.

3.8. Conclusions

The overall benefit-risk of Darzalex in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include Darzalex as a subcutaneous injection in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma, who are eligible for autologous stem cell transplant, based on the primary analysis results from the pivotal study 54767414 / MMY3014 (PERSEUS), a randomised, open-label, active-controlled, multicentre phase 3 study.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Darzalex is not similar to Talvey, Carvykti, Abecma, Farydak, Blenrep, Ninlaro and Kyprolis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Darzalex-EMEA/H/C/004077/II/72.